NOVEL PROTEINS AND NUCLEIC ACIDS ENCODING SAME

RELATED APPLICATIONS

This application claims priority to U.S. provisional application Serial No. 60/171,329, filed December 21, 1999, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The invention generally relates to nucleic acids and polypeptides encoded therefrom. More specifically, the invention relates to nucleic acids encoding novel polypeptides, as well as vectors, host cells, antibodies, and recombinant methods for producing these nucleic acids and polypeptides.

SUMMARY OF THE INVENTION

The invention is based in part upon the discovery of novel nucleic acid sequences encoding novel polypeptides. Nucleic acids encoding the polypeptides disclosed in the invention, and derivatives and fragments thereof, will hereinafter be collectively designated as "FCTRX" nucleic acid or polypeptide sequences.

In one aspect, the invention provides an isolated FCTRX nucleic acid molecule encoding a FCTRX polypeptide that includes a nucleic acid sequence that has identity to the nucleic acids disclosed in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29. In some embodiments, the FCTRX nucleic acid molecule can hybridize under stringent conditions to a nucleic acid sequence complementary to a nucleic acid molecule that includes a protein-coding sequence of a FCTRX nucleic acid sequence. The invention also includes an isolated nucleic acid that encodes a FCTRX polypeptide, or a fragment, homolog, analog or derivative thereof. For example, the nucleic acid can encode a polypeptide at least 80% identical to a polypeptide comprising the amino acid sequences of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30. The nucleic acid can be, for example, a genomic DNA fragment or a cDNA molecule that includes the nucleic acid sequence of any of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29.

Also included in the invention is an oligonucleotide, *e.g.*, an oligonucleotide which includes at least 6 contiguous nucleotides of a FCTRX nucleic acid (*e.g.*, SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29) or a complement of said oligonucleotide.

Also included in the invention are substantially purified FCTRX polypeptides (SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30). In some embodiments, the FCTRX polypeptides include an amino acid sequence that is substantially identical to the amino acid sequence of a huma FCTRX polypeptide.

The invention also features antibodies that immunoselectively-binds to FCTRX polypeptides.

In another aspect, the invention includes pharmaceutical compositions which include therapeutically- or prophylactically-effective amounts of a therapeutic and a pharmaceutically-acceptable carrier. The therapeutic can be, *e.g.*, a FCTRX nucleic acid, a FCTRX polypeptide, or an antibody specific for a FCTRX polypeptide. In a further aspect, the invention includes, in one or more containers, a therapeutically- or prophylactically-effective amount of this pharmaceutical composition.

In a further aspect, the invention includes a method of producing a polypeptide by culturing a cell that includes a FCTRX nucleic acid, under conditions allowing for expression of the FCTRX polypeptide encoded by the DNA. If desired, the FCTRX polypeptide can then be recovered.

In another aspect, the invention includes a method of detecting the presence of a FCTRX polypeptide in a sample. In the method, a sample is contacted with a compound that selectively binds to the polypeptide under conditions allowing for formation of a complex between the polypeptide and the compound. The complex is detected, if present, thereby identifying the FCTRX polypeptide within the sample.

The invention also includes methods to identify specific cell or tissue types based on their expression of a FCTRX.

Also included in the invention is a method of detecting the presence of a FCTRX nucleic acid molecule in a sample by contacting the sample with a FCTRX nucleic acid probe or primer, and detecting whether the nucleic acid probe or primer bound to a FCTRX nucleic acid molecule in the sample.

In a further aspect, the invention provides a method for modulating the activity of a FCTRX polypeptide by contacting a cell sample that includes the FCTRX polypeptide with a compound that binds to the FCTRX polypeptide in an amount sufficient to modulate the activity of said polypeptide. The compound can be, *e.g.*, a small molecule, such as a nucleic acid, peptide, polypeptide, peptidomimetic, carbohydrate, lipid or other organic (carbon containing) or inorganic molecule, as further described herein.

Also within the scope of the invention is the use of a Therapeutic in the manufacture of a medicament for treating or preventing disorders or syndromes including, *e.g.*, cancer,

neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, and hematopoietic disorders. The Therapeutic can be, *e.g.*, a FCTRX nucleic acid, a FCTRX polypeptide, or a FCTRX-specific antibody, or biologically-active derivatives or fragments thereof.

The invention further includes a method for screening for a modulator of disorders or syndromes including, *e.g.*, cancer, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, and hematopoietic disorders. The method includes contacting a test compound with a FCTRX polypeptide and determining if the test compound binds to said FCTRX polypeptide. Binding of the test compound to the FCTRX polypeptide indicates the test compound is a modulator of activity, or of latency or predisposition to the aforementioned disorders or syndromes.

Also within the scope of the invention is a method for screening for a modulator of activity, or of latency or predisposition to an disorders or syndromes including, *e.g.*, cancer, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, and hematopoietic disorders, by administering a test compound to a test animal at increased risk for the aforementioned disorders or syndromes. The test animal expresses a recombinant polypeptide encoded by a FCTRX nucleic acid. Expression or activity of FCTRX polypeptide is then measured in the test animal, as is expression or activity of the protein in a control animal which recombinantly-expresses FCTRX polypeptide and is not at increased risk for the disorder or syndrome. Next, the expression of FCTRX polypeptide in both the test animal and the control animal is compared. A change in the activity of FCTRX polypeptide in the test animal relative to the control animal indicates the test compound is a modulator of latency of the disorder or syndrome.

In yet another aspect, the invention includes a method for determining the presence of or predisposition to a disease associated with altered levels of a FCTRX polypeptide, a FCTRX nucleic acid, or both, in a subject (*e.g.*, a human subject). The method includes measuring the amount of the FCTRX polypeptide in a test sample from the subject and comparing the amount of the polypeptide in the test sample to the amount of the FCTRX polypeptide present in a control sample. An alteration in the level of the FCTRX polypeptide in the test sample as compared to the control sample indicates the presence of or predisposition to a disease in the subject. Preferably, the predisposition includes, *e.g.*, cancer, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, and hematopoietic disorders. Also, the expression levels of the new polypeptides of the invention can be used in a method to screen for various cancers.

In a further aspect, the invention includes a method of treating or preventing a pathological condition associated with a disorder in a mammal by administering to the subject a FCTRX polypeptide, a FCTRX nucleic acid, or a FCTRX-specific antibody to a subject (*e.g.*, a human subject), in an amount sufficient to alleviate or prevent the pathological condition. In preferred embodiments, the disorder, includes, *e.g.*, cancer, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, and hematopoietic disorders.

In yet another aspect, the invention can be used in a method to identity the cellular receptors and downstream effectors of the invention by any one of a number of techniques commonly employed in the art. These include but are not limited to the two-hybrid system, affinity purification, co-precipitation with antibodies or other specific-interacting molecules.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

Other features and advantages of the invention will be apparent from the following detailed description and claims.

DETAILED DESCRIPTION

The invention is based, in part, upon the discovery of novel nucleic acid sequences that encode novel polypeptides. The novel nucleic acids and their encoded polypeptides are referred to individually as FCTR1, FCTR2, FCTR3, FCTR4, FCTR5, FCTR6, FCTR7, FCTR8, FCTR9, FCTR10, FCTR11, FCTR12, FCTR13, and FCTR14. The nucleic acids, and their encoded polypeptides, are collectively designated herein as "FCTRX".

The novel FCTRX nucleic acids of the invention include the nucleic acids whose sequences are provided in Tables 1A, 2A, 3A, 4A, 5A, 6A, 7A, 8A, 9A, 10A, 11A, 12A, 13A, and 14A, inclusive ("Tables 1A - 14A"), or a fragment thereof. The invention also includes a mutant or variant FCTRX nucleic acid, any of whose bases may be changed from the corresponding base shown in Tables 1A - 14A while still encoding a protein that maintains the activities and physiological functions of the FCTRX protein fragment, or a fragment of such a nucleic acid. The invention further includes nucleic acids whose sequences are complementary to those just described, including complementary nucleic acid fragments. The invention

additionally includes nucleic acids or nucleic acid fragments, or complements thereto, whose structures include chemical modifications. Such modifications include, by way of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject. In the mutant or variant nucleic acids, and their complements, up to 20% or more of the bases may be so changed.

The novel FCTRX proteins of the invention include the protein fragments whose sequences are provided in Tables 1B, 2B, 3B, 4B, 5B, 6B, 7B, 8B, 9B, 10B, 11B, 12B, 13B, and 14B, inclusive ("Tables 1B - 14B"). The invention also includes a FCTRX mutant or variant protein, any of whose residues may be changed from the corresponding residue shown in Tables 1B - 14B while still encoding a protein that maintains its native activities and physiological functions, or a functional fragment thereof. In the mutant or variant FCTRX protein, up to 20% or more of the residues may be so changed. The invention further encompasses antibodies and antibody fragments, such as F_{ab} or $(F_{ab})_2$, that bind immunospecifically to any of the FCTRX proteins of the invention.

FCTR1 (AL031943_A)

The novel FCTR1 nucleic acid encoding a C-terminal fragment of a novel FCTR1 protein is shown in Table 1A. A "TAA" stop codon was identified at the 3' end indicating that this sequence is a coding sequence. The stop codon is shown in bold letters. This sequence originates in chromosome 6. No ATG start codon was found, indicating that the cDNA extends 5' of the disclosed sequence in Table 1A.

Table 1A. FCTR1 (AL031943_A) nucleotide fragment (SEQ ID NO:1).

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acccatcttttctcttcttcgtgctcctaaacttaggctaccaagctttgctggggaaagcactccagg
tgggtgttactacaaatcaccgtctgctgacccactggtactacctgacagcctttgatatttccagagt
caatacctgctttccattctccacagcatctaatataagtcatggcttctcatctgtcctgcttccccgc
ttcgcgttcaccactgtgctgagatatagggaaaggaatgggaacaaggaagccatcgccggcctctcca
gctctggaggcttcacagcttgcctcctccttcgtctgttgagtcatcccacacgcaaccacaactatgt
gggagattctgtgccaggctttggcaactaa
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The encoded C-terminal fragment of the encoded protein is presented using the one-letter code in Table 1B. The protein including the C-terminal fragment disclosed has a high probability of being secreted extracellularly. A signal peptide most likely is cleaved between residues 19 and 20, *i.e.*, at the dash in the amino acid sequence LLG-KAL.

Table 1B. C-terminal fragment of the encoded FCTR1 protein sequence (SEQ ID NO:2).

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THLFLFFVLLNLGYQALLGKALQVGVTTNHRLLTHWYYLTAFDISRVNTCFPFSTASNISHGFSSVLLPR
FAFTTVLRYRERNGNKEAIAGLSSSGGFTACLLLRLLSHPTRNHNYVGDSVPGFGN
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In a search of sequence databases, no similarities were found to any known expressed nucleic acid or protein. The human genomic fragment HS223B1, from clone RP1-223B1 on chromosome 6p24.1-25.3, aligned with the FCTR1 nucleotide sequence, as shown in Table 1C. Putative intron and exon information can be construed from this alignment.

Table 1C. BLASTN alignments of FCTR1 (SEQ ID NO:1) with genomic clone HS223B1

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Alignment between:
HS223B1  Human DNA sequence from clone RP1-223B1 on chromosome 6p24.1-25.3 Contains
STSs and GSSs, complete sequence. 5/2000 and (Pasted_No.:1-228)
      Length = 126281
      Score = 452.0,      bits (228.0), Expect = 1e-125
      Identities = 228/228 (100%)
      Strand = Plus / Plus

Query: 1        acccatctttttctcttcttcgtgctcctaaacttaggctaccaagctttgctggggaaa 60
                 ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 1483     acccatctttttctcttcttcgtgctcctaaacttaggctaccaagctttgctggggaaa 1542

Query: 61       gcactccaggtgggtgttactacaaatcaccgtctgctgacccactggtactacctgaca 120
                 ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 1543     gcactccaggtgggtgttactacaaatcaccgtctgctgacccactggtactacctgaca 1602

Query: 121      gcctttgatatttccagagtcaatacctgctttccattctccacagcatctaatataagt 180
                 ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 1603     gcctttgatatttccagagtcaatacctgctttccattctccacagcatctaatataagt 1662

Query: 181      catggcttctcatctgtcctgcttccccgcttcgcgttcaccactgtg 228
                 ||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 1663     catggcttctcatctgtcctgcttccccgcttcgcgttcaccactgtg 1710 (SEQ ID NO:34)

Alignment between:
HS223B1  Human DNA sequence from clone RP1-223B1 on chromosome 6p24.1-25.3 Contains
STSs and GSSs, complete sequence. 5/2000 and (Pasted_No.:226-381)
      Length = 126281
      Score = 309.0,      bits (156.0), Expect = 5e-82
      Identities = 156/156 (100%)
      Strand = Plus / Plus

Query: 226      gtgctgagatatagggaaaggaatgggaacaaggaagccatcgccggcctctccagctct 285
                 ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 4527     gtgctgagatatagggaaaggaatgggaacaaggaagccatcgccggcctctccagctct 4586

Query: 286      ggaggcttcacagcttgcctcctccttcgtctgttgagtcatcccacacgcaaccacaac 345
                 ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 4587     ggaggcttcacagcttgcctcctccttcgtctgttgagtcatcccacacgcaaccacaac 4646

Query: 346      tatgtgggagattctgtgccaggctttggcaactaa 381
                 ||||||||||||||||||||||||||||||||||
Sbjct: 4647     tatgtgggagattctgtgccaggctttggcaactaa 4682 (SEQ ID NO:35)
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The nucleic acids and proteins of the invention are potentially useful in the treatment of cancer, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, and hematopoietic disorders.

FCTR2 (AL078594_A)

The novel nucleic acid encoding a novel protein C-terminal fragment is shown in Table 2A. The initiation codon is at the 5' end, and a "TAG" stop codon was identified at the 3' end

indicating that this sequence is a coding sequence. The start and stop codons are shown in bold letters. This sequence originates in chromosome 6, in clone RP1-293L8 at map location q22.2-22.33. Homology of 100% was shown to the human genomic clone HSDJ293L8 obtained from this region, which contains the HEY2 gene for hairy/enhancer-of-split related with YRPW motif 2 (cardiovascular basic helix-loop-helix factor 1, CHF1), ESTs, STSs, GSSs and four putative CpG islands. FCTR2 nucleotide regions 1-213, 214-367, and 366-570 correspond 100% to HSDJ293L8 regions 49502-49714, 52745-52898, and 54432-54636, respectively.

Table 2A. Nucleotide sequence (SEQ ID NO:3) of FCTR2 (AL078594_A).

atgactgtcaaggctcctaaaggtcataaaggtgacataacttctatactgttagttcaaacacttgctc
agagctgccatgctgtgaggaggcccaagctagtcagctcagagagagcatctggagaggctctgaagct
acacaactatagagtcctcagctgcacaagccccctgctgttccagctccaaccactgctagactacaac
catatgatactgagtaacttagccccagacgtcagggtgccactgagtatgcagtatgctgacttaatca
taaaaattaacacctttagtattcaagcagctcatatcactcacaaatttctctttaacaaagaaaggca
tgcatttcatacacggggacaattcggtcagattgtttcttcccaatacctctatgagatcaattgcact
gaaggaatgcctatttttactagaagaacgaaggtggaagtcaataatttgaagcatggggtagcttca
gaggaggagaggttcggggatcgggtacaagacttggcttgggccaggataaaaatactcagtatgaaaa
acctgag**tag**

The encoded FCTR2 polypeptide sequence (SEQ ID NO.:4) is presented using the one-letter code in Table 2B. The protein appears not to have a strong probability of secretion. No signal peptide is predicted for this protein. No significant matches were found in a BLASTP search against the FCTR2 polypeptide.

Table 2B. Encoded FCTR2 protein sequence (SEQ ID NO:4).

MTVKAPKGHKGDITSILLVQTLAQSCHAVRRPKLVSSERASGEALKLHNYRVLSCTSPLLFQLQPLLDYN
HMILSNLAPDVRVPLSMQYADLIIKINTFSIQAAHITHKFLFNKERHAFHTRGQFGQIVSSQYLYEINCT
EGMPIFTRRTKVEVNNFEAWGSFRGGEVRGSGTRLGLGQDKNTQYEKPE

The nucleic acids and proteins of the invention are potentially useful in the treatment of cancer, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, and hematopoietic disorders.

FCTR3 (AL078595_A)

The novel nucleic acid encoding a novel protein C-terminal fragment is shown in Table 3A. The initiation codon is at the 5' end and a TGA stop codon was identified at the 3' end indicating that this sequence is a coding sequence. The start and stop codons are shown in bold letters. This sequence originates in clone RP3-399J4 on chromosome 6q15-16.3. No significant matches were found in a BLASTN search against the FCTR3 nucleotide sequence.

Table 3A. Nucleotide sequence (SEQ ID NO:5) of FCTR3 (AL078595_A).

atgccgccactgctggtcctgctcttgctcctgccgccaccacttgcacctcccctcttcagccagtgtg
gtggcagcggctgctcccgacagcccaccattcccatcagtaatatggaggggcaaatatgtgtaaagcc

ttcaggtgccaaagctgcccagaacccctggaagaattatcaaagatgcggtccctctcttcaattcca
tggtatattttgtccttcagttctgcagagcctgcaatcaaacatgctaaagcagagaaatacaataaga
gacctatacttgacattagcagaggaagtccagctgtgtacactaattatgataaacatccattcacaat
gtctgggaggagactagccacagacctggaaagaggtgaagaaaaacgacaccatgaaaaaggagcaaag
tga

The encoded protein is presented using the one-letter code in Table 3B. The protein has a high probability of extracellular secretion. A signal peptide is predicted for this protein with a cleavage site between residues 16 and 17, *i.e.*, at the dash in the amino acid sequence PLA-PPL. No significant matches were found in a BLASTP search against the FCTR3 polypeptide.

Table 3B. Encoded FCTR3 protein sequence (SEQ ID NO:6).

MPPLLVLLLLLPPPLAPPLFSQCGGSGCSRQPTIPISNMEGQICVKPSGAKAAPEPLEELSKMRSLSSIP
WYILSFSSAEPAIKHAKAEKYNKRPILDISRGSPAVYTNYDKHPFTMSGRRLATDLERGEEKRHHEKGAK

The nucleic acids and proteins of the invention are potentially useful in the treatment of cancer, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, and hematopoietic disorders.

FCTR4 (AL109627_A)

The novel nucleic acid encoding a novel transforming immortalized mammary oncogene-like protein is shown in Table 4A. An initiation codon is shown at the beginning of the sequence and a TGA stop codon was identified at the 3' end indicating that this sequence is a coding sequence. This sequence originates in chromosome 1 from clone RP4-733M16 at map location p36.11-36.23.

Table 4A. Nucleotide sequence (SEQ ID NO:7) of FCTR4 (AL109627_A).

atggccagacctcccgtgcccggttcggtggttgtcccaaactggcacgagagtgccgagggcaaggagt
acctggcttgcattctgcgcaagaaccgccggcgggtgtttgggctgcttgagcggccagtgctgctgcc
gcctgtgtccattgacactgccagctacaagatctttgtgtccgggaagagtggtgtgggcaagacggcg
ctggtggccaagctggctggcctggaggtgcctgtggtgcaccacgagaccaccggcatccagaccaccg
tggtattttggccagccaagctgcaggccagcagccgtgtcgtcatgtttcgttttgagttctgggactg
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tgccaagatggctgagctgcaggtgcgggacctgagcctgaagctgcagggcatccccggccacgtgttc
ctcctccagctcctccacgggcagcacatgaagcaccagttcctgctgcgggcccggacggaaagtgaga
agcagcgatggatctcagccttgtgcccctccagcccccaggaggacaaggaggtcatcagtgaggggga
agattgcccccaggttcagtgtgttaggacatacaaggcactgcacccagatgagctgaccttggagaag
actgacatcctgtcagtgaggacctggaccagtgacggctggctggaaggggtccgcctggcagatggtg
agaaggggtgggtgccccaggcctatgtggaagagatcagcagcctcagcgcccgcctccgaaacctccg
ggagaataagcgagtcacaagtgccaccagcaaactgggggaggctcctgtg**tga**

The encoded protein is presented using the one-letter code in Table 4B. The protein has a high probability of sorting into the plasma membrane. No signal peptide is predicted to occur for this protein.

Table 4B. Encoded FCTR4 protein sequence (SEQ ID NO:8).

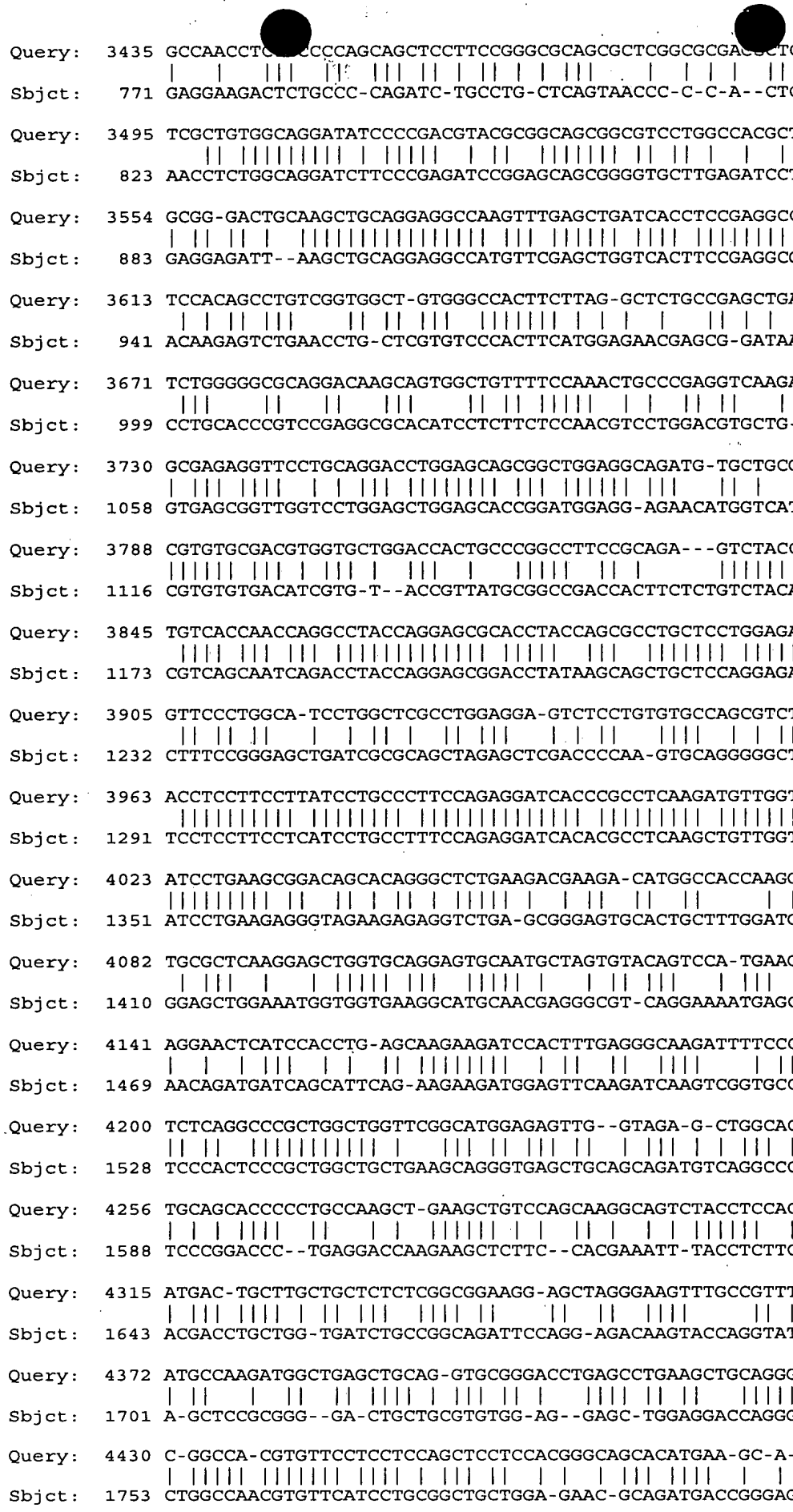
MARPPVPGSVVVPNWHESAEGKEYLACILRKNRRRVFGLLERPVLLPPVSIDTASYKIFVSGKSGVGKTA
LVAKLAGLEVPVVHHETTGIQTTVVFWPAKLQASSRVVMFRFEFWDCGESALKKFDHMLLACMENTDAFL

FLFSFTDRASFEDLPGQLARIAGEAPGVVRMVIGSKFDQYMHTDVPERDLTAFRQAWELPLLRVKSVPGR
RLADGRTLDGRAGLADVAHILNGLAEQLWHQDQTAMTPPTGRRLCLAPCGGIYVPDSRGTFSETGKPALI
KVGQSGVRPLLTVPLTPRWVRLRARLGGEAATPAAAGERRLRQRRWRENFQRNLEEGLFELPGYQVPGSD
LNSCQLLYPYWACWGYWHKYQPLDQPLDKLSCLFDHPGTVFFSIFMSFWGHGLPGALEAGSATLAHHWDC
SDFQDQEAMPSSAPHHWDCSDFQDQEVMPSSALHHWDCSDFQDQEECPHLQFAALALQMTQNPVTGLKEP
YFQPHSCLSHLLTSSAAILTVLCVVMIFLVSVIIYHGIISIAMFHTGNSVLMTQANVLWGNGGPKALSKV
LCVCQQQCGPGGCHIQVTQQLIIIMVGKQLLNHMEEFVGLGGGPGPDTPCLPELQFGFITIFVGAFLLAP
LFTLLNNRVEIGLDAHKFLCKYQRPMAGRGWTSGSDCSCWRPCELILPRTNARSRLGYWLNGQGQILGRR
RGGNAGFGVEIREPLQTPQPRYKASRDVGVNLALFYWKLLAVHVHLGFIIAFEGLMNQTLCLGGISPSQL
GRERASPAGTAKQHQQRAWAQRGPGGWQSKRGMDCGPPATLQPHLTGPPGTAHHPVAVCQQESLSFAELP
ALKPPSPVCLDLFPVAPEELRAPGSRWSLGTPAPLQGLLWPLSPGGSDTEITSGGMRPSRAGSWPHCPGA
QPPALEGPWSPRHTQPQRRASHGSEKKSAWRKMRVYQREEVPGCPEAHAVFLEPGQVVQEQALSTEEPRV
ELSGSTRVSLEGPERRRFSASELMTRLHSSLRLGRNSAARALISGSGTGAAREGKASGMEARSVEMSGDR
VSRPAPGDSREGDWSEPRLDTQEEPPLGSRSTNERRQSRFLLNSVLYQEYSDVASARELRRQQREEEGPG
DEAEGAEEGPGPPRANLSPSSSFRAQRSARGSTFSLWQDIPDVRGSGVLATLSLRDCKLQEAKFELITSE
ASYIHSLSVAVGHFLGSAELSECLGAQDKQWLFSKLPEVKSTSERFLQDLEQRLEADVLRFSVCDVVLDH
CPAFRRVYLPYVTNQAYQERTYQRLLLENPRFPGILARLEESPVCQRLPLTSFLILPFQRITRLKMLVEN
ILKRTAQGSEDEDMATKAFNALKELVQECNASVQSMKRTEELIHLSKKIHFEGKIFPLISQARWLVRHGE
LVELAPLPAAPPAKLKLSSKAVYLHLFNDCLLLSRRKELGKFAVFVHAKMAELQVRDLSLKLQGIPGHVF
LLQLLHGQHMKHQFLLRARTESEKQRWISALCPSSPQEDKEVISEGEDCPQVQCVRTYKALHPDELTLEK
TDILSVRTWTSDGWLEGVRLADGEKGWVPQAYVEEISSLSARLRNLRENKRVTSATSKLGEAPV

In a search of sequence databases, it was found, for example, that the nucleic acid sequence has 1120 of 1772 bases (63%) identical to human guanine nucleotide exchange factor Rac-GEF cDNA (patn:V99828) (SEQ ID NO: 36), as shown in Table 4C. The terms "percent identities" and "percent positives" are defined below in the Nucleic Acid section.

Table 4C. BLASTN identity search of FCTR4 and the hGEF cDNA (SEQ ID NO: 36).

```
>patn:V99828 Human guanine nucleotide exchange factor Rac-GEF cDNA - Homo sapiens,
3171 bp.
  Score = 1856 (278.5 bits), Expect = 7.2e-78, P = 7.2e-78
  Identities = 1120/1772 (63%), Positives = 1120/1772 (63%), Strand = Plus / Plus

Query:  3042 ATGACCCGGCTGCACTCTTCTCTG-CGCCTGGGGCGGAATTCAGCAGCCCGGGCACT-CA 3099
             |||| ||  ||| || |||   |  | ||||| || |||| |  |   ||  |||   ||
Sbjct:   371 ATGAGCCC-CTG-AC-CTTGAATATCCCCTGGAGCAGAATGC--CT--CCTTGCAGAACA 423

Query:  3100 TCTCTGG-GTCAGGCACCGGAGCAGCCCGGGAAGGGAAAGCATCTGGAATGGAGGCTCG- 3157
              |  ||  | ||| | || | | ||||| |||| ||  |  || |   |  |  |  |
Sbjct:   424 GCAATGCAGACAGAC-CCAG-G-AGCCCAGGAAATGAGTGAGTC-GTCCTCCACCCCGGG 479

Query:  3158 AAGTGTAGAGATGAGCGGGGACCGGGTGTCGC-GGCC-A--GCCCCTGGTGACTCAC-GA 3212
             || ||  |  | |  || |||  ||  | | | |||| |  |||||      ||||| ||
Sbjct:   480 AAATGGGGCCACGCCCGAGGAGTGGCCGGCCCTGGCCGACAGCCCCACCACGCTCACCGA 539

Query:  3213 GAGG--GCGATTGGTCCGAGCCCAGGCTAGAC-ACACAGGAAGAGCCGCCTTTGGGGTCC 3269
             |     |||  || ||| | ||||  |  | | || |  | |||  |  | |||
Sbjct:   540 GGCCCTGCGGATGATCC-ACCCCATTCCCGCCGACTCCTGGAGAAACCTCATTGAACAAA 598

Query:  3270 -AGGAGCACCA--ACGAGCGGCGCC-AG-TC--TCGATTCCTCCTT-AACTCCGTCCTCT 3321
              ||| ||  ||   |  ||      || || |   |||| || |||  || ||    | |
Sbjct:   599 TAGG-GCTCCTGTATCAGGAATACCGAGATAAATCGACTC-TCCAAGAAATCGAAAC-C- 654

Query:  3322 ATCAGGAATACAGCGACGTGGCCAGCGCCCGCGA-ACTGCGGCGGCAGCAGCGCGAG-GA 3379
             |  ||| | |||| || |  |  |  |     | | ||    | | |  | || | || ||
Sbjct:   655 AGGAGGCA-ACAG-GATGCAGAAATAGAAGACAATACCAATGGGTCCCCGGC-C-AGTGA 710

Query:  3380 GGAGGGCCCGGGGGACGAGGCCGA-G-GGCGCAG-AGGAGGGGCCGGG--GCCGCCGCGG 3434
             |||   ||||| ||| || |  || | || | || |||||| |||||   |||  |  |
Sbjct:   711 GGACACCCCGGAGGAGGAAGAAGAAGAGGAGGAGGAGGAGGAGCCGGCCAGCCCACCAGA 770
```



```
Query:  3435 GCCAACCTC CCCAGCAGCTCCTTCCGGGCGCAGCGCTCGGCGCGA CTCCACCTTC 3494
             |   |   |||  ||  ||| || | || | | |||   .  | | | |  ||| |  |||
Sbjct:   771 GAGGAAGACTCTGCCC-CAGATC-TGCCTG-CTCAGTAACCC-C-C-A--CTCAAGGTTC 822

Query:  3495 TCGCTGTGGCAGGATATCCCCGACGTACGCGGCAGCGGCGTCCTGGCCACGCTG-AGCCT 3553
              || |||||||| | |||||  | ||  ||||||| || || |  |  ||  |||||
Sbjct:   823 AACCTCTGGCAGGATCTTCCCGAGATCCGGAGCAGCGGGGTGCTTGAGATCCTACAGCCT 882

Query:  3554 GCGG-GACTGCAAGCTGCAGGAGGCCAAGTTTGAGCTGATCACCTCCGAGGCCTCCTACA 3612
             | || || |  |||||||||||||||| ||| |||||| |||| |||||||| ||||||
Sbjct:   883 GAGGAGATT--AAGCTGCAGGAGGCCATGTTCGAGCTGGTCACTTCCGAGGCGTCCTACT 940

Query:  3613 TCCACAGCCTGTCGGTGGCT-GTGGGCCACTTCTTAG-GCTCTGCCGAGCTGAGCGAGTG 3670
              | | || |||     || || |||  ||||||| | | |  |   || | | ||  ||
Sbjct:   941 ACAAGAGTCTGAACCTG-CTCGTGTCCCACTTCATGGAGAACGAGCG-GATAAGGAAGAT 998

Query:  3671 TCTGGGGGCGCAGGACAAGCAGTGGCTGTTTTCCAAACTGCCCGAGGTCAAGAGCAC-CA 3729
              |||    ||   ||   |||    || || |||||  | |  || ||   | ||  ||
Sbjct:   999 CCTGCACCCGTCCGAGGCGCACATCCTCTTCTCCAACGTCCTGGACGTGCTG-GCTGTCA 1057

Query:  3730 GCGAGAGGTTCCTGCAGGACCTGGAGCAGCGGCTGGAGGCAGATG-TGCTGCGCTTCAG- 3787
             | ||| ||||  | | ||| |||||||| ||| |||||| |||   || |   || | |
Sbjct:  1058 GTGAGCGGTTGGTCCTGGAGCTGGAGCACCGGATGGAGG-AGAACATGGTCATCT-CTGA 1115

Query:  3788 CGTGTGCGACGTGGTGCTGGACCACTGCCCGGCCTTCCGCAGA---GTCTACCTGCCCTA 3844
              |||||| ||| | ||| |  |||  |   |||||  || |       ||||||  |  ||||
Sbjct:  1116 CGTGTGTGACATCGTG-T--ACCGTTATGCGGCCGACCACTTCTCTGTCTACATCACCTA 1172

Query:  3845 TGTCACCAACCAGGCCTACCAGGAGCGCACCTACCAGCGCCTGCTCCTGGAGAACCCCAG 3904
              |||| ||| ||| ||||||||||||| |||||  |||  ||||||| ||||||  | ||
Sbjct:  1173 CGTCAGCAATCAGACCTACCAGGAGCGGACCTATAAGCAGCTGCTCCAGGAGAAGGC-AG 1231

Query:  3905 GTTCCCTGGCA-TCCTGGCTCGCCTGGAGGA-GTCTCCTGTGTGCCAGCGTCTGCCCCTT 3962
              || || ||   |  | || |  || |||   | | ||   ||||  | | ||||| |
Sbjct:  1232 CTTTCCGGGAGCTGATCGCGCAGCTAGAGCTCGACCCCAA-GTGCAGGGGGCTGCCCTTC 1290

Query:  3963 ACCTCCTTCCTTATCCTGCCCTTCCAGAGGATCACCCGCCTCAAGATGTTGGTGGAGAAC 4022
              |||||||||| |||||||| |||||||||||||| |||||||| |||||||  |||||
Sbjct:  1291 TCCTCCTTCCTCATCCTGCCTTTCCAGAGGATCACACGCCTCAAGCTGTTGGTCCAGAAC 1350

Query:  4023 ATCCTGAAGCGGACAGCACAGGGCTCTGAAGACGAAGA-CATGGCCACCAAGGCCTTCAA 4081
              ||||||||| ||  || | || | ||||| |  | ||  ||  ||      | ||   |||
Sbjct:  1351 ATCCTGAAGAGGGTAGAAGAGAGGTCTGA-GCGGGAGTGCACTGCTTTGGATGCTCACAA 1409

Query:  4082 TGCGCTCAAGGAGCTGGTGCAGGAGTGCAATGCTAGTGTACAGTCCA-TGAAGAGGACAG 4140
             | |||  |   | ||||| |||  ||||| |   | || |||   | |||   | || |
Sbjct:  1410 GGAGCTGGAAATGGTGGTGAAGGCATGCAACGAGGGCGT-CAGGAAAATGAGCCGCACGG 1468

Query:  4141 AGGAACTCATCCACCTG-AGCAAGAAGATCCACTTTGAGGGCAAGATTTTCCCGCTGATC 4199
             | | | |||  | |  || ||||||||  | ||  ||  ||||    | ||  | |||
Sbjct:  1469 AACAGATGATCAGCATTCAG-AAGAAGATGGAGTTCAAGATCAAGTCGGTGCCCATCATC 1527

Query:  4200 TCTCAGGCCCGCTGGCTGGTTCGGCATGGAGAGTTG--GTAGA-G-CTGGCACCACTGCC 4255
             || ||  |||||||||||  |   ||| || ||| ||  | ||| | | ||| |||   ||
Sbjct:  1528 TCCCACTCCCGCTGGCTGCTGAAGCAGGGTGAGCTGCAGCAGATGTCAGGCCCCAAGACC 1587

Query:  4256 TGCAGCACCCCCTGCCAAGCT-GAAGCTGTCCAGCAAGGCAGTCTACCTCCACCTCTTCA 4314
             | | | ||||  ||   | |  |||||| | |  || |  | | ||||||  ||| ||||
Sbjct:  1588 TCCCGGACCC--TGAGGACCAAGAAGCTCTTC--CACGAAATT-TACCTCTTCCTGTTCA 1642

Query:  4315 ATGAC-TGCTTGCTGCTCTCTCGGCGGAAGG-AGCTAGGGAAGTTTGCCGTTTTCGTC-C 4371
             | ||| |||| | || |||  |||| ||    ||  ||  ||||      || || | | |
Sbjct:  1643 ACGACCTGCTGG-TGATCTGCCGGCAGATTCCAGG-AGACAAGTACCAGGTATTTGACTC 1700

Query:  4372 ATGCCAAGATGGCTGAGCTGCAG-GTGCGGGACCTGAGCCTGAAGCTGCAGGGC-ATCCC 4429
             | ||   |  ||  || |||| | ||| || |   |||| || ||   |||||| |  |
Sbjct:  1701 A-GCTCCGCGGG--GA-CTGCTGCGTGTGG-AG--GAGC-TGGAGGACCAGGGCCAGACG 1752

Query:  4430 C-GGCCA-CGTGTTCCTCCTCCAGCTCCTCCACGGGCAGCACATGAA-GC-A--CCAGTT 4483
             | ||||| ||||||| |||| | ||| ||  | |  | ||| ||||  |  |  |||  |
Sbjct:  1753 CTGGCCAACGTGTTCATCCTGCGGCTGCTGGA-GAAC-GCAGATGACCGGGAGGCCACCT 1810
```

```
Query:  4484 CC-TGCTGCGGGCCCGGACGGAAAGTGAGAAGCAGCGATGGATCTCAGCCTTGTGCCCCT 4542
             | ||||   |||     |  | ||||||| | |||| ||||  |  |  || |||||
Sbjct:  1811 ACATGCTAAAGGCGTCCTCTCAGAGTGAGATGAAGCGTTGGATGACCTCACTG-GCCCC- 1868

Query:  4543 CCAGCCCCCAGGAGGAC-AAGGAGGT--CAT-CAG-TGAGGGG-GAAG-ATTGCCCCCAG 4595
             | |    | |||||||| |||   ||  | | ||  |   ||  |  | | |||||||||
Sbjct:  1869 CAA----C-AGGAGGACCAAGTTTGTTTCGTTCACATCCCGGCTGCTGGACTGCCCCCAG 1923

Query:  4596 GTTCAGTGTGTTAGGACATACAAGGCACTGCACCCAGATGAGCTGACCTTGGAGAAGACT 4655
             || ||||| ||     |||||  ||| | ||| ||||| ||||||||  |||||   |
Sbjct:  1924 GTCCAGTGCGTGCACCCATACGTGGCTCAGCAGCCAGACGAGCTGACGCTGGAGCTCGCC 1983

Query:  4656 GACATCCTGT-CAGTGAGGACCTGGACCAGTGACGGCTGGCTGGAAGGGGTCCGCCTGGC 4714
             ||||||||   ||    ||||  | ||    ||||| ||| |    || |  || ||| |
Sbjct:  1984 GACATCCTCAACATCCTGGACAAG-ACTGACGACGGGTGGATCTTTGGCGAGCGTCTG-C 2041

Query:  4715 A-GATGGTGAGAAGGGGTGGGTGCCCCAGGCCTATGTG-GAAGAGATCA-GCAGCCTCAG 4771
             | ||    ||||  || ||| | ||||||  | |||   || ||||||  | | ||  ||
Sbjct:  2042 ACGACCAGGAGAGAGGCTGGTT-CCCCAGCTCCATGACTGAGGAGATCTTGAATCCCAAG 2100

Query:  4772 CGCCCGCCTCCGAAACCTCCGGGAGAATAAGCGAGTC-ACAAG 4813
               || | | | ||| ||||  |||   |   || ||| |||||
Sbjct:  2101 ATCCGGTCCCAGAA-CCTCAAGGAATGTTTCCGTGTCCACAAG 2142
```

FCTR4 has an even higher homology to a probable guanine nucleotide regulatory protein TIM (SEQ ID NO: 37; SWISSPROT-ACC:Q12774), as shown in Table 4D. The full amino acid sequence of the FCTR4 protein was found to have 276 of 517 residues (53%), identical to, and 355 of 517 residues (68%) positive with, the 519 amino acid residue human probable guanine nucleotide regulatory protein TIM (oncogene TIM, P60 TIM, transforming immortalized mammary oncogene) from ptnr: SWISSPROT-ACC:Q12774. TIM has transforming activities in NIH/3T3 fibroblasts. See, e.g., Chan *et al.*, 1994 *Oncogene* 9: 1057-1063. The 2.3-kb TIM cDNA encodes a predicted protein of 60-kD containing a Dbl-homology (DH) domain. See, *e.g.*, Online Mendelian Inheritance in Man database accession number OMIM 600888. The DH motif is shared by several signal transducing molecules that are implicated as regulators of small GTP-binding proteins. See, OMIM 600888. Therefore, the TIM oncogene is also thought to be involved in the control of cytoskeletal organization through regulation of small GTP-binding proteins. See, e.g., Chan *et al.*, 1994; OMIM 600888.

Table 4D. BLASTX identity search of FCTR4 and hTIM protein (SEQ ID NO:37).

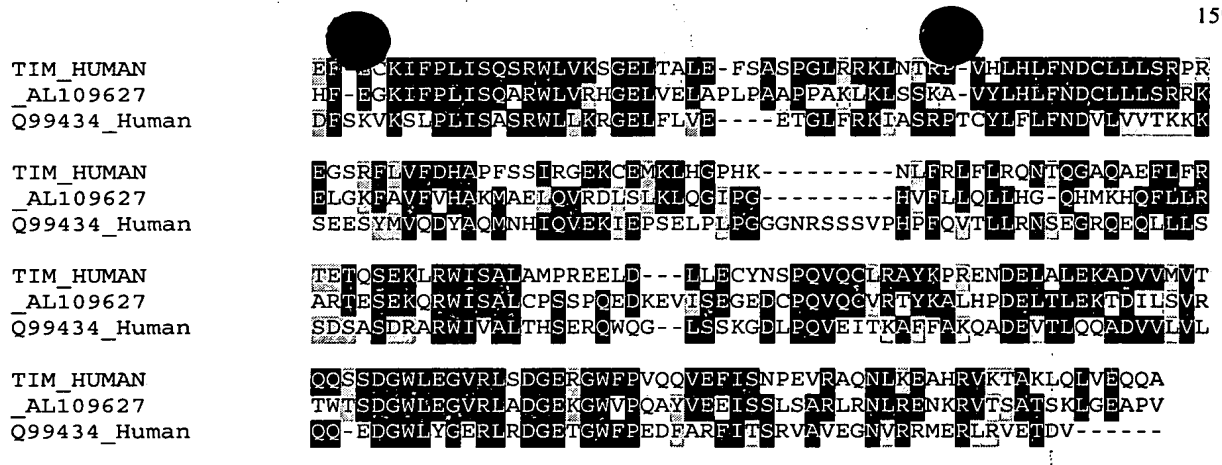
```
>ptnr:SWISSPROT-ACC:Q12774 PROBABLE GUANINE NUCLEOTIDE REGULATORY PROTEIN TIM
(ONCOGENE TIM) (P60 TIM)(TRANSFORMING IMMORTALIZED MAMMARY ONCOGENE) - Homo sapiens
(Human), 519 aa.
Score = 1275 (448.8 bits), Expect = 3.5e-129, P = 3.5e-129
Identities = 276/517 (53%), Positives = 355/517 (68%), Frame = +3

Query:  3285 RRQSRFLLNS--VLYQEYSDVASARELRRQQREEEGPGDEAEGAEEGPGPPRANLSPSSS 3458
             || |+ |+||  +|||||||||   +|++ ||| |     |  |    |  ||  |  | |
Sbjct:     6 RRCSK-LINSSQLLYQEYSDVVLNKEIQSQQRLESL--SETPGPSS-PRQPRKALVSSES 61

Query:  3459 FRAQRSARGSTFSLWQDIPDVRGSGVLATLSLRDCKLQEAKFELITSEASYIHSLSVAVG 3638
             +  || +  |+ ||||+|| || | || +++  | |||| ||||| |||||+ ||++||
Sbjct:    62 Y-LQRLSMASSGSLWQEIPVVRNSTVLLSMTHEDQKLQEVKFELIVSEASYLRSLNIAVD 120

Query:  3639 HFLGSAELSECLGAQDKQWLFSKLPEVKSTSERFLQDLEQRLEADVLRFSVCDVVLDHCP 3818
             ||  |  |   |  |+ |||||+| +|+  |  || |||+  | ++  | ||||||+| |
Sbjct:   121 HFQLSTSLRATLSNQEHQWLFSRLQDVRDVSATFLSDLEENFENNIFSFQVCDVVLNHAP 180
```

```
Query:  3819 AFRRVYLPYVTNQAYQERTYQRLLLENPRFPGILARLEESPVCQRLPLTSFLILPFQRIT 3998
             ||||||||||||| |||||+| |+  |  |  +| +||  |||||| | ||||||||||
Sbjct:   181 DFRRVYLPYVTNQTYQERTFQSLMNSNSNFREVLEKLESDPVCQRLSLKSFLILPFQRIT 240

Query:  3999 RLKMLVENILKRTAQGSEDEDMATKAFNALKELVQECNASVQSMKRTEELIHLSKKIHFE 4178
             |||+|++|||||| || +|  |||| +||++|+++|| +||||+||||||+||+|| ||
Sbjct:   241 RLKLLLQNILKRTQPGSSEEAEATKAHHALEQLIRDCNNNVQSMRRTEELIYLSQKIEFE 300

Query:  4179 GKIFPLISQARWLVRHGELVELAPLPAAPPAKLKLSSKAVYLHLFNDCLLLSRRKELGKF 4358
             |||||||+||||+ |||  |    |+|  + ||+++ |+|||||||||||| +|  +|
Sbjct:   301 CKIFPLISQSRWLVKSGELTALE-FSASPGLRRKLNTRPVHLHLFNDCLLLSRPREGSRF 359

Query:  4359 AVFVHAKMAELQVRDLSLKLQGIPGHVFLLQLLHG-QHMKHQFLLRARTESEKQRWISAL 4535
             || ||  + ++     +|| |   ++| | |     |  + +|| |  |+||| ||||||
Sbjct:   360 LVFDHAPFSSIRGEKCEMKLHGPHKNLFRLFLRQNTQGAQAEFLFRTETQSEKLRWISAL 419

Query:  4536 CPSSPQEDKEVISEGEDCPQVQCVRTYKALHPDELTLEKTDILSVRTWTSDGWLEGVRLA 4715
               + |+|+ +++ |  + |||||+| ||    ||| ||| |++ |   +|||||||||+
Sbjct:   420 --AMPREELDLL-ECYNSPQVQCLRAYKPRENDELALEKADVVMVTQQSSDGWLEGVRLS 476

Query:  4716 DGEKGWVPQAYVEEISSLSARLRNLRENKRVTSATSKLGE 4835
             |||+|| |   || ||+   | +||+|  || +|  +| |
Sbjct:   477 DGERGWFPVQQVEFISNPEVRAQNLKEAHRVKTAKLQLVE 516
```

A multiple sequence alignment for AL109627_A is given in Table 4E, with the FCTR4 protein of the invention being shown on line 2, in a ClustalW analysis comparing the protein of the invention with related protein sequences. Table 4E depicts a ClustalW alignment of the FCTR4 against proteins from a public database. Human oncogene p60 TIM (SEQ ID NO:37 ; GenBank Acc. No. Q12774) is on line one, FCTR4 (SEQ ID NO:8) is on line two, and an unknown human polypeptide (SEQ ID NO:38; Acc. No. Q99434) is on line three. Based on this alignment, black outlined amino acid residues indicate regions of conserved sequence (*i.e.*, regions that may be required to preserve structural or functional properties); grayed amino acid residues can be mutated to a residue with comparable steric and/or chemical properties without altering protein structure or function (e.g. L to V, I, or M); non-highlighted amino acid residues can potentially be mutated to a much broader extent without altering structure or function.

TABLE 4E

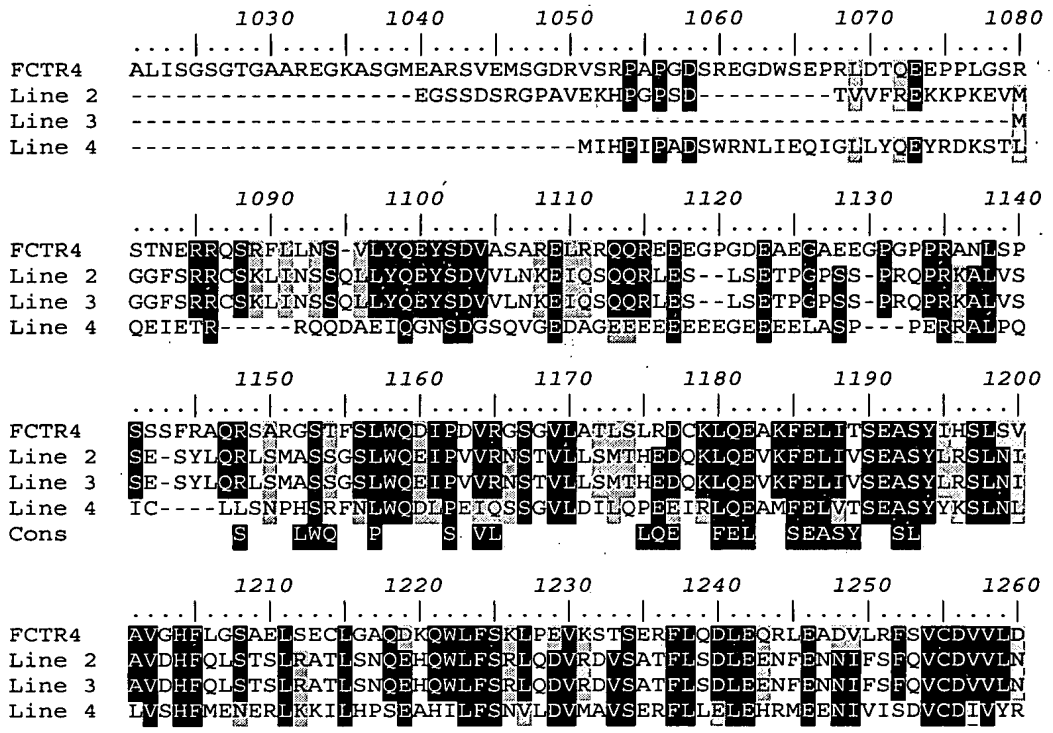
```
TIM_HUMAN       GGFSRRCSKLINSSQLLYQEYSDVVLNKEIQSQQRLES--LSETPGPSS-PRQPRKALVS
_AL109627       STNERRQSRFLLNS-VLYQEYSDVASARELRRQQREEEGPGDEAECAEEGPGPPRANLSP
Q99434_Human    ------------------------------------------------------------

TIM_HUMAN       SE-SYLQRLSMASSGSLWQEIPVVRNSTVLLSMTHEDQKLQEVKFELIVSEASYLRSLNI
_AL109627       SSSFRAQRSARGSTFSLWQDIPDVRGSGVLATLSLRDCKLQEAKFELITSEASYIHSLSV
Q99434_Human    ------------------------------------------MFEILTSEFSYQHSLSI

TIM_HUMAN       AVDHFQLSTSLRATLSNQEHQWLFSRLQDVRDVSATFLSDLEENFENNIFSFQVCDVVLN
_AL109627       AVGHFLGSAELSECLGAQDKQWLFSKLPEVKSTSERFLQDLEQRLEADVLRFSVCDVVLD
Q99434_Human    LVEEFLQSKELRATVTQMEHHHLFSNILDVLGASQRFFEDLEQRHKAQVLVEDISDILEE

TIM_HUMAN       HAPDFRRVYLPYVTNQTYQERTFQSLMNSNSNFREVLEKLESDPVCQRLSLKSFLILPFQ
_AL109627       HCPAFRRVYLPYVTNQAYQERTYQRLLLENPRFPGILARLEESPVCQRLPLTSFLILPFQ
Q99434_Human    HAEKYFHPYIAYCSNEVYQQRTLQKLISSNAAFREALREIERRPACGGLPMLSFLILPMQ

TIM_HUMAN       RITRLKLLLQNILKRTQPGSSEEAEATKAHHALEQLIRDCNNNVQSMRRTEELIYLSQKI
_AL109627       RITRLKMLVENILKRTAQGSEDEDMATKAFNALKELVQECNASVQSMKRTEELIHLSKKI
Q99434_Human    RVTRLPLLMDTLCLKTQGHSERYKAASRALKAISKLVRQCNEGAHRMERMEQMYTLHTQL
```

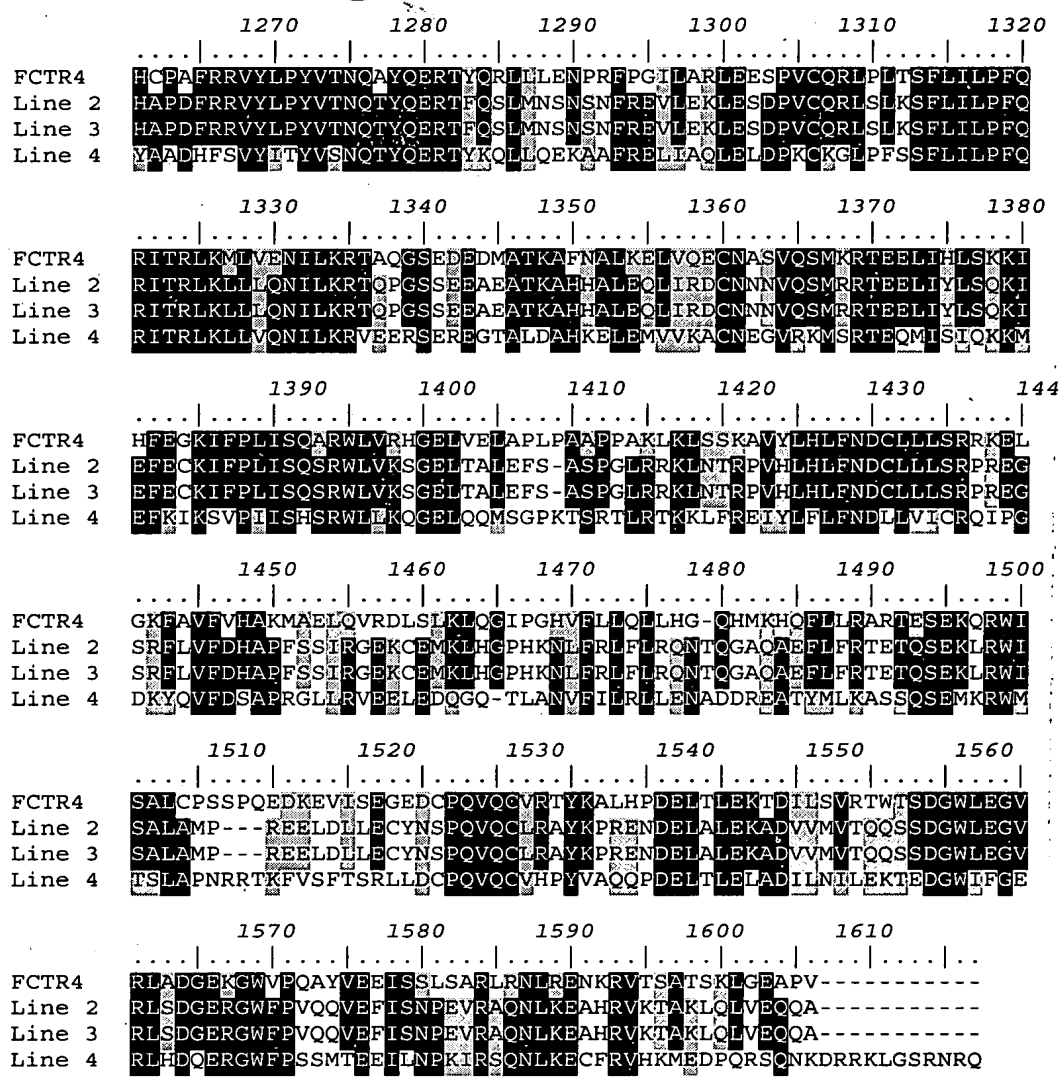


From these analyses, it is seen that the FCTR4 AL109627_A nucleic acid and protein are similar to the TIM oncogene. The transforming gene, designated TIM, encoded a predicted protein species of 60 kDa containing a Dbl-Homology (DH) motif. This motif is also present in other growth regulatory molecules including Bcr, Cdc24, Vav, Ras-grf, and Ect2 which have been implicated as regulators of small GTP-binding proteins. NIH3T3 cells transfected with TIM expression plasmid showed altered growth properties in vitro and were tumorigenic when injected into nude mice. The 6.5 kilobasepair (kb) transcript of the TIM gene was found to be expressed mainly in kidney, liver, pancreas, lung, and placenta.

Table 4F:BLAST alignment of FCTR4

```
BLAST alignment file included sequences:
      Line 2 > gi|11420361|ref|XP_004812.1| Oncogene TIM [Homo sapiens](SEQ ID NO:39)
      Line 3 > gi|4885633|ref|NP_005426.1| Oncogene TIM [Homo sapiens](SEQ ID NO:40)
      Line 4 > gi|9845277|ref|NP_063920.1| neuronal guanine nucleotide exchange
               factor [Mus musculus](SEQ ID NO:41)
```





FCTR4 was found to have high homology to the domains shown in Table 4G.

Table 4G: CD domain analysis of FCTR4

Sequences producing significant alignments:	**Score (bits)**	**E value**
Guanine nucleotide exchange factor for Rho/Rac/Cdc42-like GTPa...	110	7e-25
RhoGEF, RhoGEF domain	69.3	1e-12
ras, Ras family	61.2	4e-10
Rab subfamily of small GTPases; Rab GTPases are implicated in ...	51.2	4e-07
SH3, SH3 domain	49.7	1e-06
Rho (Ras homology) subfamily of Ras-like small GTPases; Member...	44.7	4e-05
Src homology 3 domains; Src homology 3 (SH3) domains bind to t...	43.9	6e-05
Ras subfamily of RAS small GTPases; Similar in fold and functi...	38.9	0.002
arf, ADP-ribosylation factor family	38.1	0.003

The AL109627_A nucleic acids and proteins of the invention are useful in potential therapeutic applications implicated in various cancers, tumors and similar neoplastic diseases. For example, a cDNA encoding the transforming immortalized mammary oncogene-like protein

may be useful in gene therapy, and the transforming immortalized mammary oncogene-like protein may be useful when administered to a subject in need thereof. The novel nucleic acid encoding transforming immortalized mammary oncogene-like protein, and the transforming immortalized mammary oncogene-like protein of the invention, or fragments thereof, may further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed. These materials are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods.

FCTR5 (AL109913_A)

The novel FCTR5 nucleic acid encoding a C-terminal fragment of a novel FCTR5 protein is shown in Table 5A. This sequence contains no initiation codon. A TAG stop codon was identified at the 3' end indicating that this sequence is a coding sequence. The stop codon is shown in bold letters. This sequence originates in chromosome X, clone RP11-183K14, and is found at map location q26.3-27.3.

Table 5A. FCTR5 (AL109913_A) C-terminal nucleotide fragment (SEQ ID NO:9).

```
natgatgatgagcaaaacatgatttcaatattgagcctggtgtctgtgaccattgctgtgttcatcccag
ttgcctgtgacagtcatgatcaacaagtctgcaccatgaccttctcatctccatatccagtgcccaagtt
attcctttccccaactgcaggcccccaacaggatgtgggcagcctgcatctccgctggactggagccaa
aatgccaaagcacagcaccttcgagttccatgcctccagaagggcttgtccctgcgcactgggatggtgc
ttgtttgcaaggttatagatgagaaaactgctgccttgtcggaaggaaaggtgctgtttggtctcttcgc
tggcatccccatctttaggaattccagcccaaacaagccgccttccaattag
```

The encoded C-terminal fragment of the encoded protein is presented using the one-letter code in Table 5B. The C-terminal fragment disclosed has a very high probability of being secreted extracellularly. A signal peptide most likely is cleaved between residues 28 and 29, *i.e.*, at the dash in the amino acid sequence CDS-HDQ.

Table 5B. Encoded FCTR5 polypeptide sequence (SEQ ID NO: 10).

```
XDDEQNMISILSLVSVTIAVFIPVACDSHDQQVCTMTFSSPYPVPKLFLSPTAGPPTGCGQPASPLDWSQ
NAKAQHLRVPCLQKGLSLRTGMVLVCKVIDEKTAALSEGKVLFGLFAGIPIFRNSSPNKPPSN
```

In a search of sequence databases, no similarities were found to any currently disclosed nucleic acid or protein.

The nucleic acids and proteins of the invention are potentially useful in the treatment of cancer, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, and hematopoietic disorders.

FCTR6 (AL109928_A)

A novel nucleic acid encoding a novel transmembrane protein is shown in Table 6A. It was identified in chromosome 20 clone RP4-551D2 at map location q13.2-13.33. An initiation codon is shown at the beginning of the sequence and a TAG stop codon was identified at the 3' end indicating that this sequence is a coding sequence. These are shown in bold face in Table 6A.

Table 6A. Nucleotide sequence (SEQ ID NO:11) of FCTR6 (AL109928_A).

atgagatccgggaggcacccctcgctgctgctgcttctagtgctgctgctgtggctgctgcaggtcagta
tcattgacagtgttcaacaggaaacagatgatcttactaagcaaacaaagtgtcactataagttccagga
aaagatctaccagcctctacggcgatccaagagaagatgggttatcaccaccttggagctggaggaggaa
gacccgggacccttttcccaaactcattggtgagctgttcaataatatgtcttataacatgtcactaatgt
atctaatcagtggacctggtgtggatgaatatccagagattggtttgttttctctagaagatcatgagaa
cggaaggatatatgttcaccgccctgtcgatcgagaaatgacaccatctttcacgagctggacagcaagg
gtgccttcctccagggcttccgcggggatgagcagaggccatctacgggaagggctggtgctggtttatt
ttgatgttgtggagcgctcaacaggaaaaattgtggatacatccttgattttcaacattaggatcagtga
tgtgaatgatcatgcaccccagtttccagagaaggaatttaacatcactgtgcaagaaaaccaatctgca
gggcaacctatttttcagatgttagcagtcgatttggatgaagaaaacactccaaattctcaagtccttt
acttcctcatttctcaaacaccattactgaaagaaagtggtttccgggttgatcgccttagtggagaaat
acgactctctggctgcttagattatgagaccgctcctcagtttacactgctaatcagagccagggactgt
ggagaaccgtcactgtcatccacgaccaccgttcacgtggatgtgcaagaaggcaacaaccacaggcctg
catttacccaggagaactataaggttcagattcctgaaggccgagccagccagggcgtgttgcgtctcct
ggttcaagatcgagattctccatttacatcagcttggagagcaaaattcaacatattgcatggcaatgaa
gaggggcattttgacatttcgactgaccctgagaccaacgaagggatattaaatgttatcaagcctttgg
attatgagactcgcccagcgcaaagcctcatcattgtcgtggagaatgaggagaggctcgtcttctgtga
gagaggaaagcttcagccgccaaggaaggcagcagccagcgccactgtgagtgtgcaggtgacagacgcc
aacgacccaccagcctttcacccccagagcttcattgtcaataaagaggagggcgccaggcctgggaccc
tgttgggaacttttaatgccatggatccagacagccagataagatatgaactggttcatgacccagcaaa
ttgggtcagcgtcgacaaaaactccggagtggtcatcaccgtggagccaattgaccgagaatcccctcat
gtaaataacagtttttatgtaatcatcattcacgctgttgatgatggcttcccaccgcagactgctacag
ggaccctaatgctcttcctgtctgacatcaatgacaacgtcccgactctccggccacgttcccgctacat
ggaggtctgtgagtctgctgtgcatgagcccctccacatcgaggcagaggatccggacctggagccgttc
tctgacccatttacatttgaattggacaatacctggggaaatgcggaggacacatggaagttggggagaa
attggggaaactctcctcatcaggggtaggaggctgctgggagtccctgagacatattcttgcatctgg
caagaagggtgtttccagggaagctccaggattgacgtcactgtttggcctgggtcaatcagttgaactt
ttaaccttgagaagcctgccacgtggtaattacttggtgccactcttcattggagacaaacagggacttt
cccagaagcaaactgtccatgtaaggatctgcccctgtgccagtgggctcacatgtgtggagcttgcaga
tgcagaagtggggcttcatgtgggggccctgttccctgtctgtgcagcatttgtggctctggcagtggct
ctgctttttctgttgcgatgctattttgtgcttgaacctaagaggcatggatgctctgtatccaatgatg
aaggccaccaaacactggtcatgtataatgcggagagcaaaggcacttcagcccagacatggtcagatgt
tgaaggccagaggccggctctgctcatctgcacagctgcagcaggacccacgcagggagttaaggggagg
gaaccaaagcctccaccttctaggttttggtgtatctctgggttcccttcagtgtcctgcaaatattgta
gatctcgaggaagtgcctccatctgcagcgagtcagtcagcccaagcacgctgtgctctggggagctgga
tagcacagagacccagatccacagacatgggccagatgagcaggagactgccagcagcccatcatgggaa
acaatgggcagccctgcagaatgggtgctgcctggcacctgcttcaagacaacacagacatcttctccgg
gcctagaagctttgcctaaaagcaggcaagccaggctcctgcagaaggggctgtgtacccacagactca
gggctgcagggcccttccccaggtcctgactgctgaactggaaatggggctggaggacagagaaagaaca
gaggctcttggggaggctttcatggccaggctggctgccgacctgaaggggactatctgcagagcttgg
gaagggaggcatccacagtggaatcctgtgttggaaggagccagagtccctcacactggcaggccaaaaa
ggcctggatccccaaacttttacaaaagagaaataaattcaacaacgtagcacctatagtcaacaacgta
gcatctatagtcaacaacatagcacctatagtcaacaacgtagcacctatagtcaacaacgtagcatcta
tagtcaacaacgtagcacctatagtcaacaacgtagcacctatagtcaacaacatagcacctatagtcaa
caacgtagcatctatagtcaacaatgcacttcaacattttactttaagtgctaggatacatgtgcagaag

gtgcagtctaaagagagaaatcgcttcagcctcagcaggggctgcatcatccccagggaagagccacag
ctgggcgaggattgccacaagacatttacaaggagatgatgccacggagactaacgcagactggtaaacg
gaaacacggggctttggctcgaacaccctctttcaagaaagttgtttatgaccacaaggaagtgtctctc
atctgttgggtacaaacatccccagaagatcccccgccacacattccctggatcagaacccatcagtggt
tccctagtgcctgggaatttccattcaatggcctccgaaccatgagcctgccttttctgcctgaagccca
aaaccccagctacagatctttaccccagagaccatcttgggcctccctccaggcttttgcttactctgtg
ccctcatcctggagtcctgtccccacccctatctacagaaactccaccagccctcctggctgccccgatg
gtcctcgcacagggagacttgtctacctcccgaggtcacgtgtgggctctggtcctcttgccatcatggc
agagattttgctgtatctccccctggctgctggtgctctgcttacctcctccagagttgttaacaaagag
ctgaggatgctgagctgcccagggacttggctgcaggtggca**tag**

The encoded protein is presented using the one-letter code in Table 6B. The protein has a high probability of sorting into the plasma membrane. Cleavage of a signal peptide is predicted to occur between residues 27 and 28, *i.e.*, at the dash in the sequence IDS-VQQ.

Table 6B. Encoded FCTR6 protein sequence (SEQ ID NO:12).

MRSGRHPSLLLLLVLLLWLLQVSIIDSVQQETDDLTKQTKCHYKFQEKIYQPLRRSKRRWVITTLELEEE
DPGPFPKLIGELFNNMSYNMSLMYLISGPGVDEYPEIGLFSLEDHENGRIYVHRPVDREMTPSFTSWTAR
VPSSRASAGMSRGHLREGLVLVYFDVVERSTGKIVDTSLIFNIRISDVNDHAPQFPEKEFNITVQENQSA
GQPIFQMLAVDLDEENTPNSQVLYFLISQTPLLKESGFRVDRLSGEIRLSGCLDYETAPQFTLLIRARDC
GEPSLSSTTTVHVDVQEGNNHRPAFTQENYKVQIPEGRASQGVLRLLVQDRDSPFTSAWRAKFNILHGNE
EGHFDISTDPETNEGILNVIKPLDYETRPAQSLIIVVENEERLVFCERGKLQPPRKAAASATVSVQVTDA
NDPPAFHPQSFIVNKEEGARPGTLLGTFNAMDPDSQIRYELVHDPANWVSVDKNSGVVITVEPIDRESPH
VNNSFYVIIIHAVDDGFPPQTATGTLMLFLSDINDNVPTLRPRSRYMEVCESAVHEPLHIEAEDPDLEPF
SDPFTFELDNTWGNAEDTWKLGRNWGNSPHQGVGGCWESLRHILASGKKGVSREAPGLTSLFGLGQSVEL
LTLRSLPRGNYLVPLFIGDKQGLSQKQTVHVRICPCASGLTCVELADAEVGLHVGALFPVCAAFVALAVA
LLFLLRCYFVLEPKRHGCSVSNDEGHQTLVMYNAESKGTSAQTWSDVEGQRPALLICTAAAGPTQGVKGR
EPKPPPSRFWCISGFPSVSCKYCRSRGSASICSESVSPSTLCSGELDSTETQIHRHGPDEQETASSPSWE
TMGSPAEWVLPGTCFKTTQTSSPGLEALPKSRQARLLQKGAVYPQTQGCRALPQVLTAELEMGLEDRERT
EALGEAFMARLAADLKGDYLQSLGREASTVESCVGRSQSPSHWQAKKAWIPKLLQKRNKFNNVAPIVNNV
ASIVNNIAPIVNNVAPIVNNVASIVNNVAPIVNNVAPIVNNIAPIVNNVASIVNNALQHFTLSARIHVQK
VQSKERNRFSLSRGCIIPQGRATAGRGLPQDIYKEMMPRRLTQTGKRKHGALARTPSFKKVVYDHKEVSL
ICWVQTSPEDPPPHIPWIRTHQWFPSAWEFPFNGLRTMSLPFLPEAQNPSYRSLPQRPSWASLQAFAYSV
PSSWSPVPTPIYRNSTSPPGCPDGPRTGRLVYLPRSRVGSGPLAIMAEILLYLPLAAGALLTSSRVVNKE
LRMLSCPGTWLQVA

In a search of sequence databases, it was found, for example, that the nucleic acid sequence has 225 of 381 bases (59%) identical to human cadherin-13 coding sequence (patn: :T85405) (Table 6C).

Table 6C. BLASTN identity search of FCTR6 and hCAD-13 (SEQ ID NO:42).

```
>patn:T85405 Human cadherin-13 coding sequence - Homo sapiens, 2690 bp.
 Score = 323 (48.5 bits), Expect = 6.4e-05, P = 6.4e-05
 Identities = 225/381 (59%), Positives = 225/381 (59%), Strand = Plus / Plus

Query:   804 TCCTCAGTTTACACTGCTAATCAGAG-C-CAGGGACTG--TGGA--GAACCGTC-ACTGT 856
             |||  |||  |  ||||  |  |||  |||  |  ||  |    ||  ||||  |  |    |  | |
Sbjct:  1416 TCCCAAGTATGAACTGATCATC-GAGGCTCAAGATATGGCTGGACTGGATGTTGGATTAA 1474

Query:   857 CATCCACGACCACCGTTCACGTGGATGTGCAA-GAAGGCAACAACCACAGGCCTGCATTT 915
             ||  ||||  ||||  |  ||||    |||  |  |  ||     ||  |  |||    ||    |||
Sbjct:  1475 CAGGCACGGCCACAGC-CACGATCATGATCGATGACAAAAATGATCACTCACCAAAATTC 1533

Query:   916 ACCCAGGAGAACTATAAGGTTCAGATTCCTGAAGGCCGAGCCAGCCAGGGCGTG-TTG-C 973
             |||  ||  |   |  |  |  |  |   ||  |  ||   |  |  |   ||||   |    |||  ||   |||  |
Sbjct:  1534 ACCAAGAAAGAGTTTCAAGC-CACAGTCGAGGAAG--GAGCT-GT--GGGAGTTATTGTC 1587
```

```
Query:   974 G-TCTCCTGGTTCAAGATCGAGATT-CTCCATTTACATCAGCTTGGAGAGCAAAATTCAA 1031
Sbjct:  1588 AATTTGACAGTTGAAGATAAGGATGACCCCACC-ACAGGTGCATGGAGGGCTGCCTACAC 1646

Query:  1032 CATATTGCATGGCAATGAAGAGGGGCATTTTGACATTTCGACTGACCCTGAGACCAACGA 1091
Sbjct:  1647 CATCATCAACGGAAACCCCGGGCAGAGCTTTGAAATCCACACCAACCCTCAAACCAACGA 1706

Query:  1092 AGGGATATTAAATGTTATCAAGCCTTTGGATTATGAGACT-CGCCCAGCGCAAAGCCTCA 1150
Sbjct:  1707 AGGGATGCTTTCTGTTGTCAAACCATTGGACTATGAAATTTCTGCCTTC-CACACCCTGC 1765

Query:  1151 TCATTGTCGTGGAGAATGAGGAGAGGCTCGT 1181
Sbjct:  1766 TGATCAAAGTGGAAAATGAAGACCCACTCGT 1796
```

The full amino acid sequence of the protein was found to have 155 of 413 residues (37%), identical to, and 233 of 413 residues (56%) positive with, human neural-cadherin precursor (n-cadherin) having a total of 906 amino acid residues (SWISSPROT-ACC:P19022) (Table 6D).

Table 6D. BLASTX comparison of FCTR6 and human N-cadherin (SEQ ID NO:43).

```
>ptnr:SWISSPROT-ACC:P19022 NEURAL-CADHERIN PRECURSOR (N-CADHERIN) - Homo sapiens
(Human), 906 aa.
 Score = 706 (248.5 bits), Expect = 1.3e-87, Sum P(3) = 1.3e-87
 Identities = 155/413 (37%), Positives = 233/413 (56%), Frame = +1

Query:   514 GKIVDTSLIFNIRISDVNDHAPQFPEKEFNITVQENQSAGQPIFQMLAVDLDEENTPNSQ 693
Sbjct:   244 GNQVENPIDIVINVIDMNDNRPEFLHQVWNGTVPEGSKPGTYVMTVTAIDADDPNALNGM 303

Query:   694 VLYFLISQTPLLKESG-FRVDRLSGEI-RLSGCLDYETAPQFTLLIRARDC-GEPS--LS 858
Sbjct:   304 LRYRIVSQAPSTPSPNMFTINNETGDIITVAAGLDREKVQQYTLIIQATDMEGNPTYGLS 363

Query:   859 STTTVHVDVQEGNNHRPAFTQENYKVQIPEGRASQGVLRLLVQDRDSPFTSAWRAKFNIL 1038
Sbjct:   364 NTATAVITVTDVNDNPPEFTAMTFYGEVPENRVDIIVANLTVTDKDQPHTPAWNAVYRIS 423

Query:  1039 HGNEEGHFDISTDPETNEGILNVIKPLDYETRPAQSLIIVVENEERLVFCERGKLQPPRK 1218
Sbjct:   424 GGDPTGRFAIQTDPNSNDGLVTVVKPIDFETNRMFVLTVAAENQVPLA---KGIQHPPQ- 479

Query:  1219 AAASATVSVQVTDANDPPAFHPQSFIVNKEEGARPGTLLGTFNAMDPD----SQIRYELV 1386
Sbjct:   480 --STATVSVTVIDVNENPYFAPNPKIIRQEEGLHAGTMLTTFTAQDPDRYMQQNIRYTKL 537

Query:  1387 HDPANWVSVDKNSGVVITVEPIDRESPHVNNSFYVIIIHAVDDGFPPQTATGTLMLFLSD 1566
Sbjct:   538 SDPANWLKIDPVNGQITTIAVLDRESPNVKNNIYNATFLASDNGIPPMSGTGTLQIYLLD 597

Query:  1567 INDNVPTLRPRSRYMEVCESAVHEPLHIEAEDPDLEPFSDPFTFELDNTWGNAEDTWKLG 1746
Sbjct:   598 INDNAPQVLPQEA--ETCETPDPNSINITALDYDIDPNAGPFAFDLPLSPVTIKRNWTIT 655

Query:  1747 R 1749
Sbjct:   656 R 656
```

A multiple sequence alignment for FCTR6 AL109928_A is given in Table 6E, with the protein of the invention being shown on line 4, in a ClustalW analysis comparing the protein of the invention with related protein sequences.

Table 6E. BLASTX comparison of FCTR6 and human pre-N-cadherin (SEQ ID NO:44).

```
>ptnr:SWISSPROT-ACC:P19022 NEURAL-CADHERIN PRECURSOR (N-CADHERIN) - Homo sapiens
(Human), 906 aa.
Score = 151 (53.2 bits), Expect = 1.3e-87, Sum P(3) = 1.3e-87
 Identities = 31/82 (37%), Positives = 49/82 (59%), Frame = +1

Query:   157 LRRSKRRWVITTLELEEEDPGPFPKLIGELFNNMSYNMSLMYLISGPGVDEYPEIGLFSL 336
             |+|  ||  |||   +  | |    ||||+ +   + ++    |+||  | ++|||  |+ |   |+| +
Sbjct:   154 LQRQKRDWVIPPINLPENSRGPFPQELVRIRSDRDKNLSLRYSVTGPGADQ-PPTGIFII 212

Query:   337 EDHENGRIYVHRPVDREMTPSF 402
                 +|++  | +|+|||     |
Sbjct:   213 NPI-SGQLSVTKPLDREQIARF 233
```

The FCTR6 nucleotide sequence has two regions (nucleotides 1315-1757 and 1875-2305) identical to (100%) the 1808 bp human cadherin-like protein VR20 mRNA (VR20) (GenBank AF169690). Table 6F shows a partial BlastN alignment of FCTR6 with VR20.

Table 6G. BlastN alignment of FCTR6 nucleotide with VR20 mRNA (SEQ ID NO:45).

```
>Homo sapiens cadherin-like protein VR20 mRNA, partial cds (GenBank AF169690)

                1270      1280      1290      1300      1310      1320
           ....|....|....|....|....|....|....|....|....|....|....|....|
FCTR6      AACGACCCACCAGCCTTTCACCCCCAGAGCTTCATTGTCAATAAAGAGGAGGGCGCCAGG
hVR20      ------------------------------------------------------CCAGG

                1330      1340      1350      1360      1370      1380
           ....|....|....|....|....|....|....|....|....|....|....|....|
FCTR6      CCTGGGACCCTGTTGGGAACTTTTAATGCCATGGATCCAGACAGCCAGATAAGATATGAA
hVR20      CCTGGGACCCTGTTGGGAACTTTTAATGCCATGGATCCAGACAGCCAGATAAGATATGAA

                1390      1400      1410      1420      1430      1440
           ....|....|....|....|....|....|....|....|....|....|....|....|
FCTR6      CTGGTTCATGACCCAGCAAATTGGGTCAGCGTCGACAAAAACTCCGGAGTGGTCATCACC
hVR20      CTGGTTCATGACCCAGCAAATTGGGTNAGCGTCGACAAAAACTCCGGAGTGGTCATCACC

                1450      1460      1470      1480      1490      1500
           ....|....|....|....|....|....|....|....|....|....|....|....|
FCTR6      GTGGAGCCAATTGACCGAGAATCCCCTCATGTAAATAACAGTTTTTATGTAATCATCATT
hVR20      GTGGAGCCAATTGACCGAGAATCCCCTCATGTAAATAACAGTTTTTATGTAATCATCATT

                1510      1520      1530      1540      1550      1560
           ....|....|....|....|....|....|....|....|....|....|....|....|
FCTR6      CACGCTGTTGATGATGGCTTCCCACCGCAGACTGCTACAGGGACCCTAATGCTCTTCCTG
hVR20      CACGCTGTTGATGATGGCTTCCCACCGCAGACTGCTACAGGGACCCTAATGCTCTTCCTG

                1570      1580      1590      1600      1610      1620
           ....|....|....|....|....|....|....|....|....|....|....|....|
FCTR6      TCTGACATCAATGACAACGTCCCGACTCTCCGGCCACGTTCCCGCTACATGGAGGTCTGT
hVR20      TCTGACATCAATGACAACGTCCCGACTCTCCGGCCACGTTCCCGCTACATGGAGGTCTGT

                1630      1640      1650      1660      1670      1680
           ....|....|....|....|....|....|....|....|....|....|....|....|
FCTR6      GAGTCTGCTGTGCATGAGCCCCTCCACATCGAGGCAGAGGATCCGGACCTGGAGCCGTTC
hVR20      GAGTCTGCTGTGCATGAGCCCCTCCACATCGAGGCAGAGGATCCGGACCTGGAGCCGTTC

                1690      1700      1710      1720      1730      1740
           ....|....|....|....|....|....|....|....|....|....|....|....|
FCTR6      TCTGACCCATTTACATTTGAATTGGACAATACCTGGGGAAATGCGGAGGACACATGGAAG
hVR20      TCTGACCCATTTACATTTGAATTGGACAATACCTGGGGAAATGCGGAGGACACATGGAAG

                1750      1760      1770      1780      1790      1800
           ....|....|....|....|....|....|....|....|....|....|....|....|
FCTR6      TTGGGGAGAAATTGGGGAAACTCTCCTCATCAGGGGGTAGGAGGCTGCTGGGAGTCCCTG
hVR20      TTGGGGAGAAATTGGGG----------------------------------------
```

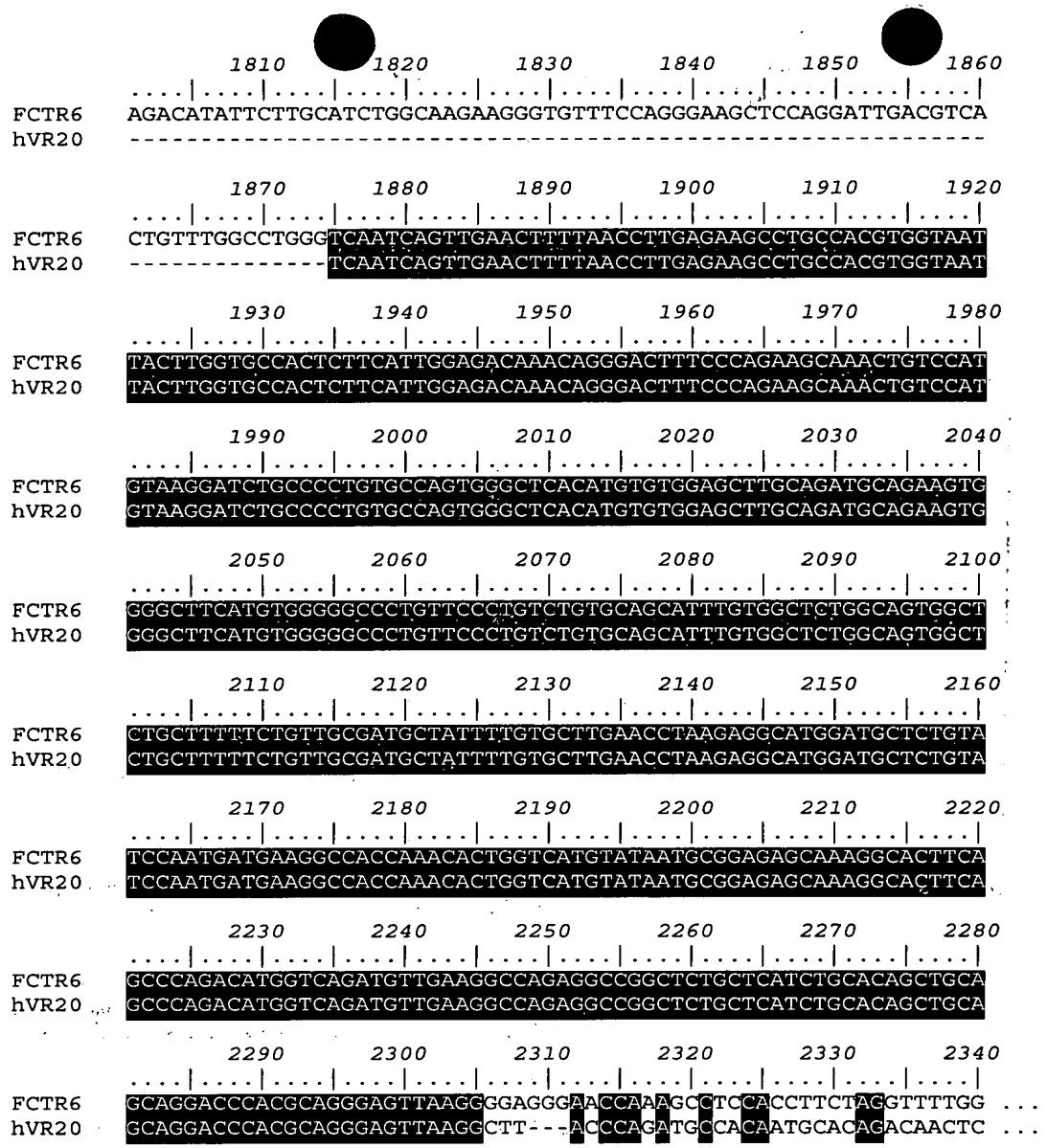
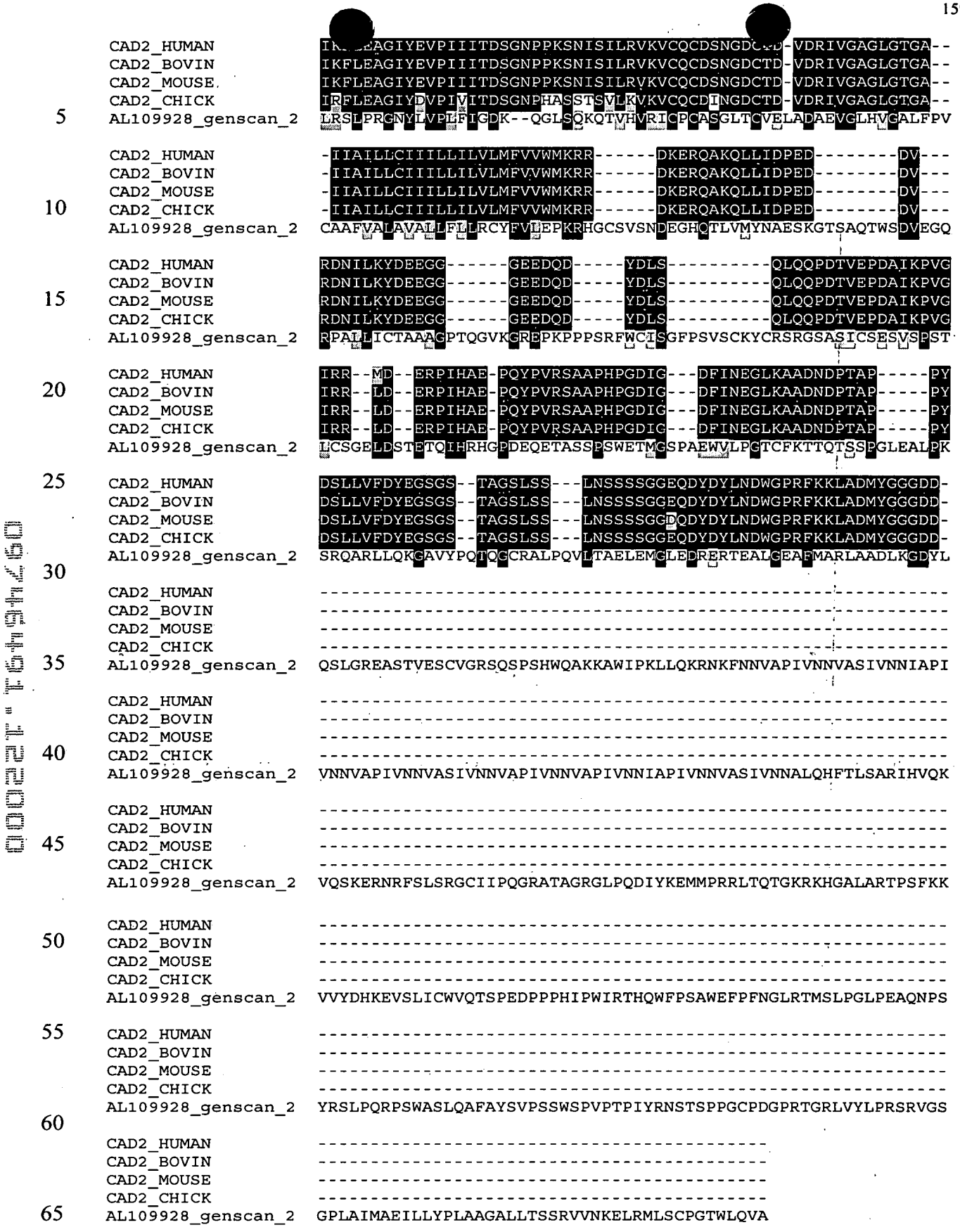


Table 6G shows a ClustalW alignment of FCTR6 with related proteins found in public databases. FCTR6 polypeptide is on line 5, human CAD2 (SEQ ID NO:46) is on line 1, bovine CAD2 (SEQ ID NO:47) is on line 2, mouse CAD2 (SEQ ID NO:48) is on line 3, and chicken CAD2 (SEQ ID NO:49) is on line 4. Based on this alignment, black outlined amino acid residues indicate regions of conserved sequence (i.e., regions that may be required to preserve structural or functional properties); grayed amino acid residues can be mutated to a residue with comparable steric and/or chemical properties without altering protein structure or function (e.g. L to V, I, or M); non-highlighted amino acid residues can potentially be mutated to a much broader extent without altering structure or function.

Table 6G. ClustalW alignment including FCTR6 (AL109928_A) protein.

```
CAD2_HUMAN          MCRIAGALRTLLP-----LLLALLQASVEASGEIALCKTGFPEDVYSAVLSKDVHEGQPL
CAD2_BOVIN          ----------------------------------SLCKTGFPEDVYSAVLSRDVLEGQPL
CAD2_MOUSE          MCRIAGGRGTLLP-----LLAALLQASVEASGEIALCKTGFPEDVYSAVLPKDVHEGQPL
CAD2_CHICK          MCRIAGTPPRILPPLALMLLAALQQAPIKATCEDMLCKMGFPEDVHSAVVSRSVHGGQPL
AL109928_genscan2   _MRSG-----RHP----------------------SLLLLLVLLLWLLQVSIIDSVQQETD
```

```
CAD2_HUMAN          LNVKFSNCNGKRKVQYESSEPADFKVDEDGMVYAVRSFPLSSE-HAKFLIVAQDKETQEK
CAD2_BOVIN          LNVKFSNCNGKRKVQYESSEPADFKVDEDGMVYAVRSFPLSSE-HSKFLIYAQDKETQEK
CAD2_MOUSE          LNVKFSNCNRKRKVQYESSEPADFKVDEDGTVYAVRSFPLTAF-QAKFLIVAQDKETQEK
CAD2_CHICK          LNVRFQSCDENRKIYFGSSEPEDFRVGEDGVVYAERSFQLSAE-PTEFVVSARDKETQEE
AL109928_genscan_2  DLTKQTKCH--YKFQEKIYQP--LRRSKR--RWVITTLELEEEDPGPFPKLIGELFNNMS

CAD2_HUMAN          WQVAVKLSLKPTLTEESVKESAEVEEIVFPRQFSKHSGHLQRQKRDWVIPPINLPENSRG
CAD2_BOVIN          WQVAVKLSLKPALPEDSVKESREIEEIVFPRQVTKHNGYLQRQKRDWVIPPINLPENSRG
CAD2_MOUSE          WQVAVNLSREPTLTEEPMKEPHEIEEIVFPRQLAKHSGALQRQKRDWVIPPINLPENSRG
CAD2_CHICK          WQMKVKLTPEPAFTGASEKDQKKIEDITFPWQQYKDSSHLKRQKRDWVIPPINLPENSRG
AL109928_genscan_2  YNMSLMYLIS----GPGVDEYPEIG--LFSLEDHENG-------RIYVHRPVDR-EMTPS

CAD2_HUMAN          PFPQELVRIRSDRDKNLSLRYSVTGPGADQPPTGIFIINPISGQLSVTKPLDREQIARFH
CAD2_BOVIN          PFPQELVRIRSDRDKNLSLRYSVTGPGADQPPTGIFIINPISGQLSVTKPLDRELIARFH
CAD2_MOUSE          PFPQELVRIRSDRDKNLSLRYSVTGPGADQPPTGIFIINPISGQLSVTKPLDRELIARFH
CAD2_CHICK          PFPQELVRIRSDRDKSLSLRYSVTGPGADQPPTGIFIINPISGQLSVTKPLDREQIASFH
AL109928_genscan_2  -FTSWTARVPSSR----------ASAGMSR------------GHL-----REGLVLVYFD

CAD2_HUMAN          LRAHAVDINGNQVENPIDIVINVIDMNDNRPEFLHQVWNGTVPEGSKPGTYVMTVTAIDA
CAD2_BOVIN          LRAHAVDINGNQVENPIDIVINVIDMNDNRPEFLHQVWNGTVPEGSKPGTYVMTVTAIDA
CAD2_MOUSE          LRAHAVDINGNQVENPIDIVINVIDMNDNRPEFLHQVWNGSVPEGSKPGTYVMTVTAIDA
CAD2_CHICK          LRAHAVDVNGNQVENPIDIVINVIDMNDNRPEFLHQVWNGTVPEGSKPGTYVMTVTAIDA
AL109928_genscan_2  VVERST---GKLVDTSLIFNIRISDVNDHAPQFPEKEFNITVQENQSAGQPIFQMLAVDL

CAD2_HUMAN          DDPNALNGMLRYRIVSQAPSTPSPNMFTINNETGDIITVAAGLDREKVQQYTLIIQATDM
CAD2_BOVIN          DDPNALNGMLRYRILSQAPSTPSPNMFTINNETGDIITVAAGLDREKVQQYTLIIQATDM
CAD2_MOUSE          DDPNALNGMLRYRILSQAPSTPSPNMFTINNETGDIITVAAGLDREKVQQYTLIIQATDM
CAD2_CHICK          DDPNAQNGMLRYRILSQAPSSPSPNMFTINNETGDIITVAAGLDREKVQQYTLIIQATDM
AL109928_genscan_2  DEENTPNSQVLYFLISQTPLLK-ESGFRVDRLSGEIR-LSGCLDYETAPQFTLLIRARDC

CAD2_HUMAN          EGNPTYGLSNTATAVITVTDWNDNPPEETAMTFYGEVPENRVDIIVANLTVTDKDQPHTP
CAD2_BOVIN          EGNPTYGLSNTATAVITVTDWNDNPPEETAMTFYGEVPENRVDVIVANLTVTDKDQPHTP
CAD2_MOUSE          EGNPTYGLSNTATAVITVTDWNDNPPEETAMTFYGEVPENRVDVIVANLTVTDKDQPHTP
CAD2_CHICK          EGNPTYGLSNTATAVITVTDWNDNPPEETAMTFYGEVPENRVDVIVANLTVTDKDQPHTP
AL109928_genscan_2  -GEPS--LSSTTTVHVDVQEGNNHRPAFTQENYKVQIPEGRASQGVLRLLVQDRDSPFTS

CAD2_HUMAN          AWNAVYRISGGDPTGRFAIQTDPNSNDGLVTVVKPIDFETNRMFVLTVAAENQ---VPLA
CAD2_BOVIN          AWNAIYRISGGDPAGRFAIQTDPNSNDGLVTVVKPIDFETNRMYVLTVAAENQ---VPLA
CAD2_MOUSE          AWNAAYRISGGDPTGRFAILTDPNSNDGLVTVVKPIDFETNRMFVLTVAAENQ---VPLA
CAD2_CHICK          AWNARYQMTGGDPTGQFTILTDPNSNDGLVTVVKPIDFETNRMFVLTVAAENQ---VPLA
AL109928_genscan_2  AWRAKFNILHGNEEGHFDISTDPETNEGILNVIKPLDYETRPAQSLIIVVENEERLVFCE

CAD2_HUMAN          KGIQHPPQ---STATVSVTVIDVNENPYFAPNPKIIRQEEGLHAGTMLTTFTAQDPDRYM
CAD2_BOVIN          KGIQHPPQ---STATVSVTVIDVNENPYFAPNPKIIRQEEGLHAGTVLTTFTAQDPDRYM
CAD2_MOUSE          KGIQHPPQ---STATVSVTVIDVNENPYFAPNPKIIRQEEGLHAGTMLTTLTAQDPDRYM
CAD2_CHICK          KGIQHPPQ---STATVSITVIDVNESPYFVPNPKLVRQEEGLLAGSMLTTFTARDPDRYM
AL109928_genscan_2  RGKLQPPRKAAASATVSVQVTDANDPPAFHPQSFIVNKEEGARPGTLLGTFNAMDPD---

CAD2_HUMAN          QQN-IRYTKLSDPANWLKIDPVNGQITTIAVLDRESPNVKNNIYNATFLASDNGIPPMSG
CAD2_BOVIN          QQN-IRYTKLSDPANWLKIDSVNGQITTIAVLDRESPNVKANIYNATFLASDNGIPPMSG
CAD2_MOUSE          QQN-IRYTKLSDPANWLKIDPVNGQITTIAVLDRESPYVQNNIYNATFLASDNGIPPMSG
CAD2_CHICK          QQTSLRYSKLSDPANWLKIDPVNGQITTTAVLDRESIYVQNNMYNATFLASDNGIPPMSG
AL109928_genscan_2  -SQ-IRYELVHDPANWVSVDKNSGVVITVEPIDRESPHVNNSFYVIIIHAVDDGFPPQTA

CAD2_HUMAN          TGTLQIYLLDINDNAPQVLPQE--AETCETPDPNSINITALDYDIDPNAGPFAFDLP---
CAD2_BOVIN          TGTLQIYLLDINDNAPQVLPQE--AEICETPDPNSINITALDYDIDPNAGPFAFDLP---
CAD2_MOUSE          TGTLQIYLLDINDNAPQVLPQE--AETCETPEPNSINIAALDYDIDPNAGPFAFDLP---
CAD2_CHICK          TGTLQIYLLDINDNAPQVNPKE--ATTCETLQPNAINITAVDPDIDPNAGPFAFELP---
AL109928_genscan_2  TGTLMLFLSDINDNVPTLRPRSRYMEVCESAVHEPLHIEAEDPDLEPFSDPFTFELDNTW

CAD2_HUMAN          ---LSPVTIKRNWT-------------------------ITRLNGDFAQLN--------LK
CAD2_BOVIN          ---LSPVTIKRNWT-------------------------ITRLNGDFAQLN--------LK
CAD2_MOUSE          ---LSPVTIKRNWT-------------------------INRLNGDFAQLN--------LK
CAD2_CHICK          ---DSPPSIKRNWT-------------------------IVRISGDHAQLS--------LR
AL109928_genscan_2  GNAEDTWKLGRNWGNSPHQGVGGCWESLRHILASGKKGVSREAPGLTSLFGLGQSVELLT
```



From these analyses, it is seen that the FCTR6 AL109928_A nucleic acid and protein a weak resemblance to neural cadherin, and a strong resemblance across a portion of FCTR6 with

human cadherin-like VR20. Cadherins are calcium dependent cell adhesion proteins. They preferentially interact with themselves in a homophilic manner in connecting cells; cadherins may thus contribute to the sorting of heterogeneous cell types. N-cadherin may be involved in neuronal recognition mechanism. They are type I membrane proteins.

Finally, FCTR6 was found to have high homology to the domains shown in Table 6H.

Table 6H: CD domain analysis of FCTR4

Sequences producing significant alignments:	**Score (bits)**	**E value**
cadherin, Cadherin domain	73.9	5e-14
cadherin, Cadherin domain	57.0	6e-09
cadherin, Cadherin domain	44.3	4e-05
cadherin, Cadherin domain	40.4	6e-04
Cadherin repeats.; Cadherins are glycoproteins involved in Ca2...	56.6	8e-09
Cadherin repeats.; Cadherins are glycoproteins involved in Ca2...	49.3	1e-06

The nucleic acids and proteins of the invention are potentially useful in the treatment of cancer, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, and hematopoietic disorders.

FCTR7 (AL109953_A)

The novel FCTR7 nucleic acid encoding a novel secreted FCTR7 protein is shown in Table 7A1. This sequence contains an initiation codon at the 5' end, and a TGA stop codon was identified at the 3' end indicating that this sequence is a coding sequence. An alternative novel FCTR7A nucleic acid encoding a novel secreted protein is shown in Table 7A2. This sequence contains an initiation codon at the 5' end, a frameshift at position 61, and a TAA stop codon indicating that this sequence is a coding sequence. The start and stop codons for both sequences are shown in bold letters. These sequences originate in chromosome 20 clone RP4-746H2.

Table 7A1. FCTR7 (AL109953_A) nucleotide sequence (SEQ ID NO:13).

atgggatgcagactgctgaccctgctgtgtttcctacaacctgcttccagctcctcgtggctctttggct
cccaatccagagctttcgcgaacaccagagcccctgtgcctctccctgcagctggctgggagttccaggg
cattaacacagacagtctttgcccatcagccagtgactgtatggagcttggatgtgaatacacagctcct
gcatccctccgaggcatctccacaccgtctcccagagaatgtctcgtaaaagctgctcctcttggggagg
ctctgggctttggagagagcacctggaattccccactagaaaagcccaaaaac**tga**

Table 7A2. Alternative FCTR7A (AL109953_A) nucleotide sequence (SEQ ID NO:29).

atgggatgcagactgctgaccctgctgtgtttcctacaacctgcttccagctcctcgtggtctttggctc
ccaatccagagctttcgcgaacaccagagcccctgtgcctctccctgcagctggctgggagttccagggc
attaacacagacagtctttgcccatcagccagtgactgtatggagcttggatgtgaatacacagctcctg
catccctccgaggcatctccacaccgtctcccagagaatgtctcg**taa**aagctgctcctcttggggaggc
tctgggctttggagagagcacctggaattccccactagaaaagcccaaaaactga

The encoded FCTR7 protein is presented using the one-letter code in Table 7B1. The FCTR7 protein has a low probability of being secreted extracellularly, although a signal peptide most likely is cleaved between residues 17 and 18, *i.e.* at the dash in the sequence ASS-SSW. The encoded FCTR7A protein is presented using the one-letter code in Table 7B2.

Table 7B. FCTR7 protein sequence (SEQ ID NO:14) encoded by SEQ ID NO:13.

MGCRLLTLLCFLQPASSSSWLFGSQSRAFANTRAPVPLPAAGWEFQGINTDSLCPSASDCMELGCEYTAP
ASLRGISTPSPRECLVKAAPLGEALGFGESTWNSPLEKPKN

Table 7B. FCTR7A protein sequence (SEQ ID NO:30) encoded by SEQ ID NO:29.

MGCRLLTLLCFLQPASSSSWSLAPNPELSRTPEPLCLSLQLAGSSRALTQTVFAHQPVTVWSLDVNTQLL
HPSEASPHRLPENVS

In a search of sequence databases, no similarities were found to known nucleic acid or protein.

The nucleic acids and proteins of the invention are potentially useful in the treatment of cancer, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, and hematopoietic disorders.

FCTR8 (AL110115_A)

The novel nucleic acid encoding a novel secreted protein is shown in Table 8A. This sequence contains an initiation codon at the 5' end, and a TAG stop codon was identified at the 3' end indicating that this sequence is a coding sequence. This sequence originates in chromosome 20 clone RP3-324O17.

Table 8A. FCTR8 (AL110115_A) nucleotide sequence (SEQ ID NO:15).

atgaagctccttcttctgcttttgactgttactctgctcctggcccaggtcaccccaggtctgccagcca
tgaaacttctttacctgtttcttgccatccttctggccatagaagaaccagtgatatcagtagagtgttg
gatggatggacactgccggttgttgtgcaaagatggtgaagacagcatcatacgctgccgaaatcgtaaa
cggtgctgtgttcctagtcgttatttaacaatccaaccagtaacaattcatggaatccttggctggacca
ctcctcagatgtccacaacagctccaaaaatgaagacaaatataactaatagata**g**

The encoded protein is presented using the one-letter code in Table 8B. The protein has a moderate probability of sorting to the plasma membrane. A signal peptide most likely is cleaved between residues 43 and 44, *i.e.* at the dash in the sequence VIS-VEC.

Table 8B. Encoded FCTR8 protein sequence (SEQ ID NO:16).

MKLLLLLLTVTLLLAQVTPGLPAMKLLYLFLAILLAIEEPVISVECWMDGHCRLLCKDGEDSIIRCRNRK
RCCVPSRYLTIQPVTIHGILGWTTPQMSTTAPKMKTNITNR

In a search of sequence databases, the BLASTN comparison revealed 91 of 129 bases (70%), out of a total of 413 bases, are identical to an unidentified human secreted protein. No similarities of significance were identified at the amino acid level.

Table 8C. BLASTN of FCTR8 with (SEQ ID NO:50).

```
Query:    28 ATGAAGCTCCTTCTTCTGCTTTTGACTGTTACT-CTGCTCCTGGCCCAGGTCACCCCAGG 86
             ||||||||||||| | |||  |||||||||  || ||||||  |  |||||  |  ||  |||||
Sbjct:    43 ATGAAGCTCCTTTTGCTGACTTTGACTGTG-CTGCTGCTCTTATCCCAGCTGACTCCAGG 101

Query:    87 TCTGCCAGCCATGAAACTTCTTTACCTGTTTCTTGCCA-T-CC-TT-CTG--GC-CATAG 139
             |  ||  | |||  | | | ||  |  | ||| | || | | || || | |  || |  ||
Sbjct:   102 TG-GC-ACCCAA-AGA-TGCTGGAA-TCTTTATGGCAAATGCCGTTACAGATGCTCCAAG 156

Query:   140 AAG-AACCAGTGATAT 154
             ||| ||  |||  |||
Sbjct:   157 AAGGAAAGAGTC-TAT 171
```

The nucleic acids and proteins of the invention are potentially useful in the treatment of cancer, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, and hematopoietic disorders.

FCTR9 (AL117336_A)

The novel nucleic acid encoding a novel secreted protein is shown in Table 9A. This sequence contains an initiation codon at the 5' end, and a TAG stop codon was identified at the 3' end indicating that this sequence is a coding sequence. The start and stop codons are indicated in bold type. This sequence originates in chromosome 10 clone RP11-324I22.

Table 9A. FCTR9 (AL117336_A) nucleotide sequence (SEQ ID NO:17).

atggcaaaggaggggcccaggagcccttgagaccgctgggcttgctgcctccccgcattctggcccagt
gctgcttggtcactctggctgtgcctccagcaggcccagctctcaacgctggctgcacggtcaagacc**ta**
g

The encoded protein is presented using the one-letter code in Table 9B. The protein has a moderate probability of sorting to the plasma membrane. A signal peptide most likely is cleaved between residues 43 and 44, *i.e.*, the dash in the amino acid sequence GCT-VKT.

Table 9B. Encoded FCTR9 protein sequence (SEQ ID NO:18).

MAKEGPQEPLRPLGLLPPRILAQCCLVTLAVPPAGPALNAGCTVKT

In a search of sequence databases no similarities of significance were identified at either the nucleic acid or the amino acid level.

The nucleic acids and proteins of the invention are potentially useful in the treatment of cancer, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, and hematopoietic disorders.

FCTR10 (AL118509_A)

The novel nucleic acid encoding a novel secreted protein is shown in Table 10A. This sequence contains an initiation codon at the 5' end, and a TAG stop codon was identified at the

3' end indicating that this sequence is a coding sequence. The start and stop codons are shown in bold type. This sequence originates in chromosome 20 clone RP4-770C23.

Table 10A. FCTR10 (AL118509_A) nucleotide sequence (SEQ ID NO:19)

atgcactcactgcggttcctactgcttttgtggttgctgtttcctctgtcactgctatccttctcttccc
ctacagtagggtttctggactgcggcacagttgtcacttcagaccaggtaagggctctattaattatgtt
ctatgaatcacaatcagatttaaaaacaaacaaaaataaaacaaaacaaaaacaaaaagagaagggaag
gagcggtctgtgaacgttaacaaatggaaatccactggggatcagcctctgtcagaactaagctccagga
aggaggaggttcagccagttgaggagccagtatcattatcagaagggaatttaggaaaaagcaagaaggt
gatgaagaatgagagggaggaagaaaagaaggaaaaggaacaaacttccagcttctcacaattccccttct
gaaagacgtacactgcccatggcaaggcacgctggatatgggttaagtaaccccaatctgaaaatccaaa
atccaaaatgctacaacatcccaaatgttttgagtgccaatgtgatgatcaatggaaatgttcac**tag**

The encoded protein is presented using the one-letter code in Table 10B. The protein has a high probability of being secreted extracellularly. A signal peptide most likely is cleaved between residues 27 and 28, *i.e.* at the dash in the sequence TVG-FLD.

Table 10B. Encoded FCTR10 protein sequence (SEQ ID NO:20).

MHSLRFLLLLWLLFPLSLLSFSSPTVGFLDCGTVVTSDQVRALLIMFYESQSDLKTNKNKTKQKQKREGK
ERSVNVNKWKSTGDQPLSELSSRKEEVQPVEEPVSLSEGNLGKSKKVMKNEREEEKKEKEQTSSFSQFPS
ERRTLPMARHAGYGLSNPNLKIQNPKCYNIPNVLSANVMINGNVH

In a search of sequence databases, the BLASTN comparison (see Table 10C) revealed 90 of 117 bases (76%), in a large genomic fragment originating on chromosome 6q23.1-24.3, are identical to a human DNA sequence containing the MEKK5 (ASK1, MAPKKK5) gene for MAP/ERK kinase kinase 5 (Mitogen Activated Protein kinase kinase kinase 5), as well as ESTs, GSSs and a putative CpG island. No similarities of significance were identified at the amino acid level.

Table 10C. BLASTN of FCTR10 with MEKK5.

```
>gb:GENBANK-ID:HS325F22|acc:AL024508 Human DNA sequence from clone 325F22 on
chromosome 6q23.1-24.3. Contains the MEKK5 (ASK1, MAPKKK5) gene for MAP/ERK kinase
kinase 5 (Mitogen Activated Protein kinase kinase kinase 5), ESTs, GSSs and a putative
CpG island, complete sequence - Homo sapiens, 154788 bp.
   Score = 330 (49.5 bits), Expect = 1.9e-10, Sum P(2) = 1.9e-10
   Identities = 90/117 (76%), Positives = 90/117 (76%), Strand = Plus / Plus

Query:    444 AAGGCACGCTGGATATGG--GTTAAGTAACCCCAATCTGAAAATCCAAAATCCAAAATGC 501
              ||||||| ||| | ||    ||| |||||||| |||   ||||||  ||||| |||||||
Sbjct: 145356 AAGGCACACTGTAAATACAAGTTGAGTAACCCTAATAAAAAAATCTGAAATCTAAAATGC 145415

Query:    502 TACAACATCCCAAATGTTTTGAGTGCCAATGTGATGATCAATGGAAATGTTCACTAG 558
              | ||| |||| |||  ||||||||||||  ||||| |||| ||||||| ||| | |
Sbjct: 145416 TCCAAAATCCAAAACTTTTTGAGTGCCAACATGATGCTCAAAGGAAATGCTCATTGG 145472 (SEQ ID
NO:51)

 Score = 163 (24.5 bits), Expect = 1.9e-10, Sum P(2) = 1.9e-10
 Identities = 69/96 (71%), Positives = 69/96 (71%), Strand = Plus / Plus

Query:    145 GAATCACAATCAGATTTAAAAACAAACAAAAATAAAA-CAAAA-CAAAAACAAAAAAGAG 202
              || | | | || | | | |||| |||||||| |||| ||||| ||||||||||||  ||
Sbjct: 29978 GAGTGAGACTCCG-TCTCAAAA-AAACAAAAACAAAAACAAAAACAAAAACAAAAACAAG 30035

Query:    203 AAGGGAAGGAGCGGTCTGTGAACGTTAACAAATGGAAA 240
```

```
              ||   | | | | | | ||| ||  |||||| |||
Sbjct: 30036 AA---ATGCATCCATAT-T-AAC-TTC-CAAATGCAAA 30066  (SEQ ID NO:52)

 Score = 121 (18.2 bits), Expect = 1.4e-08, Sum P(2) = 1.4e-08
 Identities = 57/86 (66%), Positives = 57/86 (66%), Strand = Plus / Plus

Query:    94 GGCACAGTTGTCACTTCAGACCAGGT-A-AGGGCTCTATT-AATTATGTTCTATGAATCA 150
             |||||  || | ||||  ||   | | | |  ||| || | ||  |  ||    ||||
Sbjct: 13513 GGCACTATTTT-ACTTT-GAGGTGATTACATTGCTTTACTCAAAGAACTTGGTGGAATGG 13570

Query:   151 CAATCAGATTTAAAAACAAACAAAAATAA 179
             | |  || |||||||||||||||| |||
Sbjct: 13571 CTAA-AGTTTTAAAAACAAACAAAACTAA 13598  (SEQ ID NO:53)

 Score = 117 (17.6 bits), Expect = 2.0e-08, Sum P(2) = 2.0e-08
 Identities = 27/30 (90%), Positives = 27/30 (90%), Strand = Plus / Plus

Query:   171 CAAAAATAAAACAAAACAAAAACAAAAAAG 200
             ||||||||||||||||||||  || ||||
Sbjct: 101741 CAAAAATAAAACAAAACAAAAG-AATAAAG 101769  (SEQ ID NO:54)
```

The nucleic acids and proteins of the invention are potentially useful in the treatment of cancer, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, and hematopoietic disorders.

FCTR11 (AL118522_A_EXT)

The novel nucleic acid encoding a novel K+ channel-like protein is shown in Table 11A. This sequence contains an initiation codon at the 5' end, and a TAA stop codon was identified near the 3' end indicating that this sequence is a coding sequence. The start and stop codons are shown in bold type and a putative 3'UTR is underlined. This sequence originates in chromosome 20 and was assembled as a consensus extension using the 8 sequences FCTR11 AL118522_genscan_2+, est:gb_AA283204+, est:gb_AI091631-, est:gb_AI097455+, est:gb_AI690321+, est:gb_AI739096+, est:gb_AI968607+, and est:gb_AW073155+.

Table 11A. FCTR11 (AL118522_A_EXT) nucleotide sequence (SEQ ID NO:21).

ATGCGGAGGCCGAGCGTGCGCGCGGCCGGGCTGGTCCTGTGCACCCTGTGTTACCTGCTGGTGGGCGCTG
CTGTCTTCGACGCGCTCGAGTCCGAGGCGGAAAGCGGCCGCCAGCGACTGCTGGTCCAGAAGCGGGGCGC
TCTCCGGAGGAAGTTCGGCTTCTCGGCCGAGGACTACCGCGAGCTGGAGCGCCTGGCGCTCCAGGCTGAG
CCCCACCGCGCCGGCCGCCAGTGGAAGTTCCCCGGCTCCTTCTACTTCGCCATCACCGTCATCACTACCA
TCGAGTACGGCCACGCCGCGCCGGGTACGGACTCCGGCAAGGTCTTCTGCATGTTCTACGCGCTCCTGGG
CATCCCGCTGACGCTGGTCACTTTCCAGAGCCTGGGCGAACGGCTGAACGCGGTGGTGCGGCGCCTCCTG
TTGGCGGCCAAGTGCTGCCTGGGCCTGCGGTGGACGTGCGTGTCCACGGAGAACCTGGTGGTGGCCGGGC
TGCTGGCGTGTGCCGCCACCCTGGCCCTCGGGGCCGTCGCCTTCTCGCACTTCGAGGGCTGGACCTTCTT
CCACGCCTACTACTACTGCTTCATCACCCTCACCACCATCGGCTTCGGCGACTTCGTGGCACTGCAGAGC
GGCGAGGCGCTGCAGAGGAAGCTCCCCTACGTGGCCTTCAGCTTCCTCTACATCCTCCTGGGGCTCACGG
TCATTGGCGCCTTCCTCAACCTGGTGGTCCTGCGCTTCCTCGTTGCCAGCGCCGACTGGCCCGAGCGCGC
TGCCCGCACCCCCAGCCCGCGCCCCCCGGGGGCGCCCGAGAGCCGTGGCCTCTGGCTGCCCCGCCGCCCG
GCCCGCTCCGTGGGCTCCGCCTCTGTCTTCTGCCACGTGCACAAGCTGGAGAGGTGCGCCCGCGACAACC
TGGGCTTTTCGCCCCCCTCGAGCCCGGGGGTCGTGCGTGGCGGGCAGGCTCCCAGGCTTGGGGCCCGGTG
GAAGTCCATCTGACAACCCCACCCAGGCCAGGGTCGAATCTGGAATGGGAGGGTCTGGCTTCAGCTATCA
GGGCACCCTCCCCAGGGATTGGAAACGGATGACGGGCCTTTAGGCGGTTTTTTGCCACGAGCAGTTTTTC

ATTACTGTCTGTGGCTAAGTCCCCTCCCTCCTTTCCAAAAATATATTACAGTCACCCCATAAGCCCAAAA
AAAAAAAAAAAAAAAAAAAAAAAAA

The encoded protein is presented using the one-letter code in Table 11B. The protein has a high probability of being sorted to the plasma membrane. A signal peptide most likely is cleaved between residues 23 and 24, *i.e.* at the dash in the sequence VGA-AVF.

Table 11B. Encoded FCTR11 protein sequence (SEQ ID NO:22).

MRRPSVRAAGLVLCTLCYLLVGAAVFDALESEAESGRQRLLVQKRGALRRKFGFSAEDYRELERLALQAE
PHRAGRQWKFPGSFYFAITVITTIEYGHAAPGTDSGKVFCMFYALLGIPLTLVTFQSLGERLNAVVRRLL
LAAKCCLGLRWTCVSTENLVVAGLLACAATLALGAVAFSHFEGWTFFHAYYYCFITLTTIGFGDFVALQS
GEALQRKLPYVAFSFLYILLGLTVIGAFLNLVVLRFLVASADWPERAARTPSPRPPGAPESRGLWLPRRP
ARSVGSASVFCHVHKLERCARDNLGFSPPSSPGVVRGGQAPRLGARWKSIXQPHPGQGRIWNGRVWLQLS
GHPPQGLETDDGPLGGFLPRAVFHYCLWLSPLPPFQKYITVTP

In a search of sequence databases, the BLASTN comparison (see Table 11C) revealed 641 of 854 bases (75%), in a complete coding sequence of 2590 bases, are identical to a human mRNA encoding TWIK-related acid-sensitive K+ channel (TASK) (GenBank-ID:AF006823). In a BLASTX comparison it was found that the full amino acid sequence of the protein has 168 of 258 residues (65%), identical to, and 200 of 258 residues (77%) positive with, mouse CTBAK having a total of 409 amino acid residues (SPTREMBL-ACC:O35111) (Table 11D).

Table 11C. BLASTN of FCTR11 with TWIK (SEQ ID NO:55).

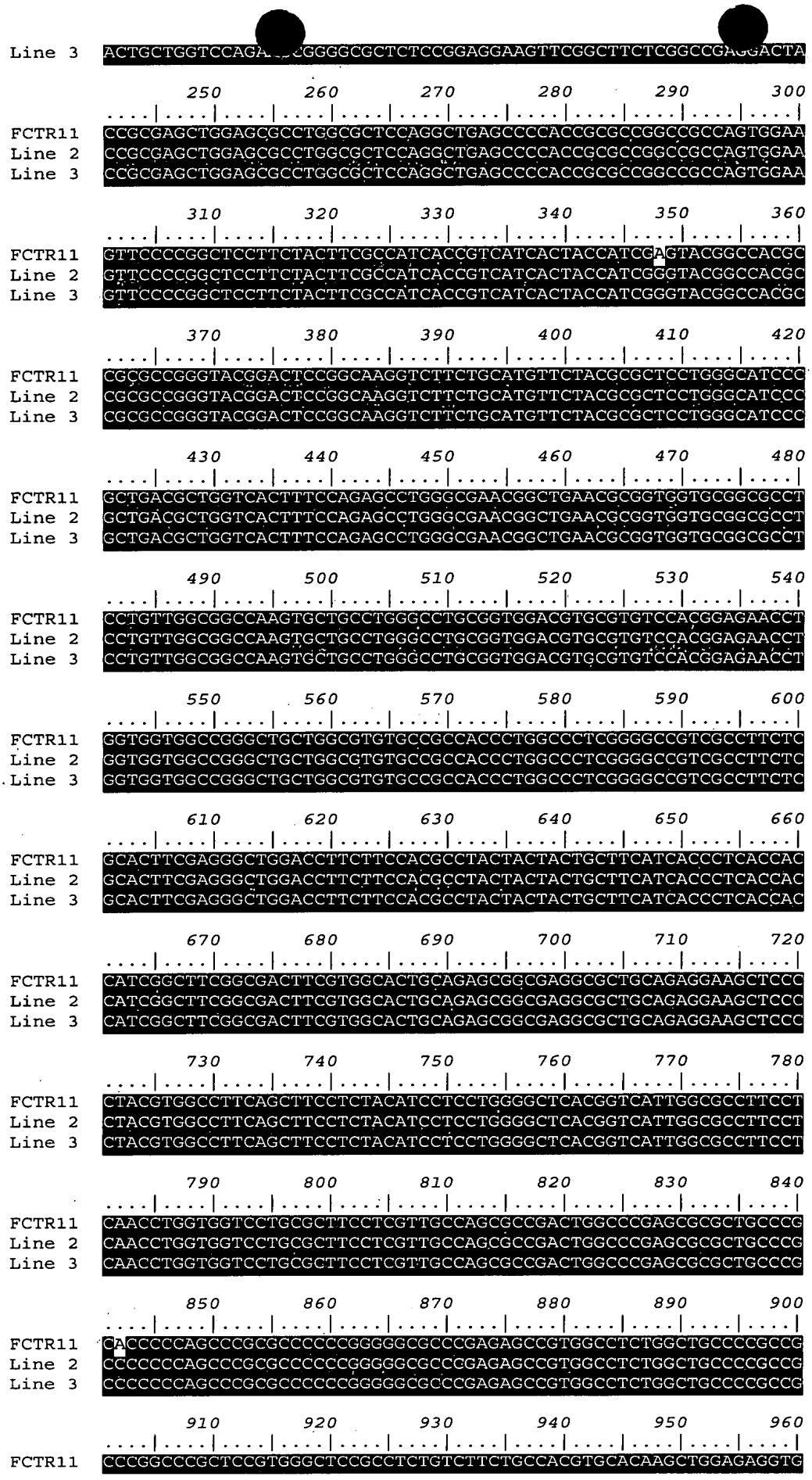
```
>gb:GENBANK-ID:AF006823|acc:AF006823 Homo sapiens TWIK-related acid-sensitive K+
channel (TASK) mRNA,
         complete cds - Homo sapiens, 2590 bp (RNA).
 Score = 2097 (314.6 bits), Expect = 4.2e-89, P = 4.2e-89
 Identities = 641/854 (75%), Positives = 641/854 (75%), Strand = Plus / Plus

Query:     1 ATGCGGAGGCCGAGCGTGCGCGCGGCCGG-GCTGGTCCTGTGCACCCTGTGTTACCTGCT 59
             |||  | ||| || ||||||| || | || |||  || ||||||||  |    ||||||||
Sbjct:   126 ATGAAGCGGCAGAACGTGCGCACG-CTGGCGCTCATCGTGTGCACCTTCACCTACCTGCT 184

Query:    60 GGTGGGCGCTGCTGTCTTCGACGCGCTCGAGTCCGAGGCGGAAA-G--CGGCCGCCAGCG 116
             |||||.|||| || |||||||||||||| ||||| ||| | ||   |  ||  || |||||
Sbjct:   185 GGTGGGCGCCGCGGTCTTCGACGCGCTGGAGTCGGAGCCCGAGCTGATCGAGCGGCAGCG 244

Query:   117 ACTGCTGGTCCAGAAGCGGGGCGCTCTCCGGAGGAAGTTCGGCTTCTCGGCC-GAG-GAC 174
             |||  | | | | ||| ||  |||   |||  |   | |  |  ||| ||| | | | |
Sbjct:   245 GCTGGAGCTGCGGCAGCAGGA-GCTG--CGGGCGCGCTACAAC--CTCAGCCAGGGCGGC 299

Query:   175 TACCGCGAGCTGGAGCGCCTGGCGCTCCAGGCTGA-GCCCCACCGCGCCGGCCGCCAGTG 233
             |||   |||||||||||| | | ||| | | || | ||| |||   ||||||   |||||
Sbjct:   300 TACGAGGAGCTGGAGCGCGTCGTGCTGC-GCCTCAAGCCGCACAAGGCCGGCGTGCAGTG 358

Query:   234 GAAGTTCCCCGGCTCCTTCTACTTCGCCATCACCGTCATCACTACCATCGAGTACGGCCA 293
             |   ||| |||||||||||||||||||||||||||||||||| |||||||  ||||| ||
Sbjct:   359 GCGCTTCGCCGGCTCCTTCTACTTCGCCATCACCGTCATCACCACCATCGGCTACGGGCA 418

Query:   294 CGCCGCGCCGGGTACGGACTCCGGCAAGGTCTTCTGCATGTTCTACGCGCTCCTGGGCAT 353
             ||| || ||  | |||||  |||||||| ||||||||||||||||||| ||||||||
Sbjct:   419 CGCGGCACCCAGCACGGATGGCGGCAAGGTGTTCTGCATGTTCTACGCGCTGCTGGGCAT 478

Query:   354 CCCGCTGACGCTGGTCACTTTCCAGAGCCTGGGCGAACGGCTGAACGCGGTGGTGCGGCG 413
             |||||| ||||| |||| |||||||||||||||| ||  | ||| |  ||||| ||
Sbjct:   479 CCCGCTCACGCTCGTCATGTTCCAGAGCCTGGGCGAGCGCATCAACACCTTGGTGAGGTA 538
```

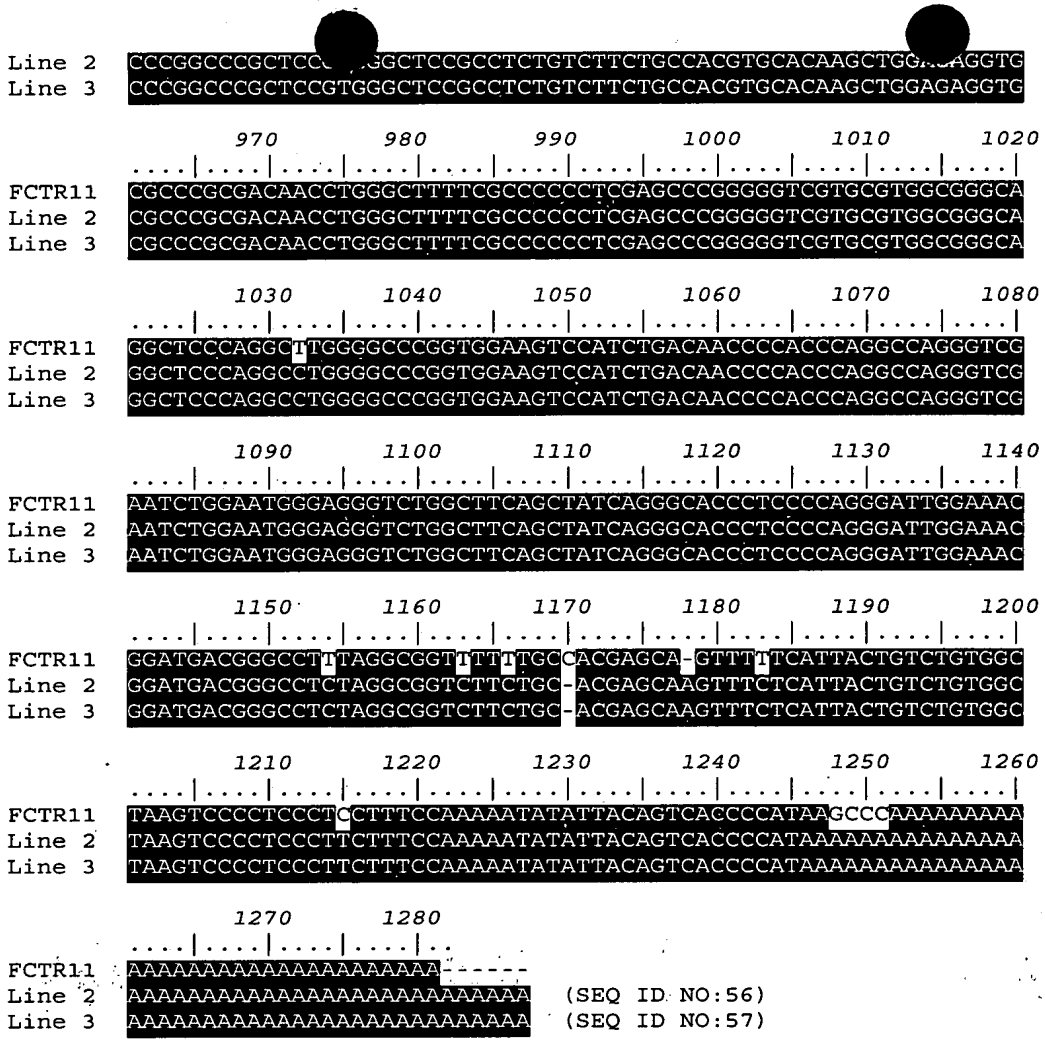
```
Query:   414 CCTCCTGTTCCG-GCCAAGTGCTGCCTGGGCCTGCGGTG-GACGTGCGTGTCCACGGAG 471
Sbjct:   539 CCTGCTGCAC-CGCGCCAAGAAGGGGCTGGGCATGCGGCGCGCCGA-CGTGTCCATGGCC 596

Query:   472 AACCTGGTGGTGGCCGGGCTGCTGG-CGTGTGCCGCCACCCTGGCCCTCGGGGCCGTCGC 530
Sbjct:   597 AACATGGTGCTCATCGG-CTTCTTCTCGTGCATCAGCACGCTGTGCATCGGCGCCGCCGC 655

Query:   531 CTTCTCGCACTTCGAGGGCTGGACCTTCTTCCACGCCTACTACTACTGCTTCATCACCCT 590
Sbjct:   656 CTTCTCCCACTACGAGCACTGGACCTTCTTCCAGGCCTACTACTACTGCTTCATCACCCT 715

Query:   591 CACCACCATCGGCTTCGGCGACTTCGTGGCACTGCAGAGCGGCGAGGCGCTGCAGAGGAA 650
Sbjct:   716 CACCACCATCGGCTTCGGCGACTACGTGGCGCTGCAGAAGGACCAGGCCCTGCAGACGCA 775

Query:   651 GCTCCCCTACGTGGCCTTCAGCTTCCTCTACATCCTCCTGGGGCTCACGGTCATTGGCGC 710
Sbjct:   776 GCCGCAGTACGTGGCCTTCAGCTTCGTCTACATCCTTACGGGCCTCACGGTCATCGGCGC 835

Query:   711 CTTCCTCAACCTGGTGGTCCTGCGCTTCCTCGTTGCCAGCGCCGACTGGCCCGA-GCGCG 769
Sbjct:   836 CTTCCTCAACCTCGTGGTGCTGCGCTTCATGACCATGAACGCCGAG-GACGAGAAGCGCG 894

Query:   770 CTGCCC-GCACC-C-C-CAGCCCGCGCCCCCCGGG--GGCGCCCGAGAGCCGTGGCCTCT 823
Sbjct:   895 ACGCCGAGCACCGCGCGCTGCTCACGCGCAACGGGCAGGCGGGCGGCGGCGGAGGGGG-T 953

Query:   824 GGCTGCCCCGC-CGCC-CGG-C-CCGC 846
Sbjct:   954 GGCAGCGC-GCACACTACGGACACCGC 979
```

Strong homology was found between FCTR11 and the human mRNA encoding the two pore potassium channel KT3.3, as shown in Table 11D. The FCTR11 nucleic acid is on line 1, the KT3.3 mRNA (GenBank gi|11641274|ref||NM_022358.1 Homo sapiens two pore potassium channel KT3.3 (LOC64181),mRNA) is on line 2, and the KT3.3 complete mRNA (GenBank gi|11228685|gb|AF257081.1|AF257081 Homo sapiens two pore potassium channel KT3.3 mRNA, complete) is on line 3.

Table 11D. BLASTN of FCTR11 nucleotide with human KT3.

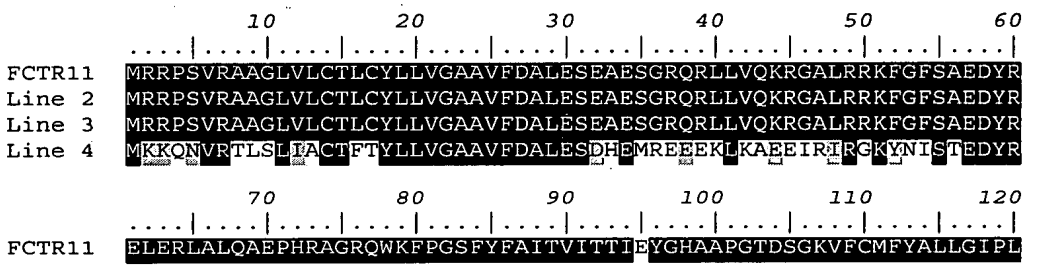
```
Line 2 > gi|11641274|ref||NM_022358.1| KT3.3 (LOC64181),mRNA
Line 3 > gi|11228685|gb|AF257081.1|AF257081 channel KT3.3 mRNA, complete
          10        20        30        40        50        60
....|....|....|....|....|....|....|....|....|....|....|....|
FCTR11  ------------------------------------------------------------
Line 2  GGAGCGCGCGGTCCGGGCACACGGAGCAGGTTGGGACCGCGGCGGGTACCGGGGCCGGGG
Line 3  GGAGCGCGCGGTCCGGGCACACGGAGCAGGTTGGGACCGCGGCGGGTACCGGGGCCGGGG

          70        80        90        100       110       120
....|....|....|....|....|....|....|....|....|....|....|....|
FCTR11  ----ATGCGGAGGCCGAGCGTGCGCGCGGCCGGGCTGGTCCTGTGCACCCTGTGTTACCT
Line 2  CGCCATGCGGAGGCCGAGCGTGCGCGCGGCCGGGCTGGTCCTGTGCACCCTGTGTTACCT
Line 3  CGCCATGCGGAGGCCGAGCGTGCGCGCGGCCGGGCTGGTCCTGTGCACCCTGTGTTACCT

          130       140       150       160       170       180
....|....|....|....|....|....|....|....|....|....|....|....|
FCTR11  GCTGGTGGGCGCTGCTGTCTTCGACGCGCTCGAGTCCGAGGCGGAAAGCGGCCGCCAGCG
Line 2  GCTGGTGGGCGCTGCTGTCTTCGACGCGCTCGAGTCCGAGGCGGAAAGCGGCCGCCAGCG
Line 3  GCTGGTGGGCGCTGCTGTCTTCGACGCGCTCGAGTCCGAGGCGGAAAGCGGCCGCCAGCG

          190       200       210       220       230       240
....|....|....|....|....|....|....|....|....|....|....|....|
FCTR11  ACTGCTGGTCCAGAAGCGGGGCGCTCTCCGGAGGAAGTTCGGCTTCTCGGCCGAGGACTA
Line 2  ACTGCTGGTCCAGAAGCGGGGCGCTCTCCGGAGGAAGTTCGGCTTCTCGGCCGAGGACTA
```


Line 3 ACTGCTGGTCCAGA CGGGGCGCTCTCCGGAGGAAGTTCGGCTTCTCGGCCGAGGACTA
250 260 270 280 290 300
FCTR11 CCGCGAGCTGGAGCGCCTGGCGCTCCAGGCTGAGCCCCACCGCGCCGGCCGCCAGTGGAA
Line 2 CCGCGAGCTGGAGCGCCTGGCGCTCCAGGCTGAGCCCCACCGCGCCGGCCGCCAGTGGAA
Line 3 CCGCGAGCTGGAGCGCCTGGCGCTCCAGGCTGAGCCCCACCGCGCCGGCCGCCAGTGGAA
310 320 330 340 350 360
FCTR11 GTTCCCCGGCTCCTTCTACTTCGCCATCACCGTCATCACTACCATCGAGTACGGCCACGC
Line 2 GTTCCCCGGCTCCTTCTACTTCGCCATCACCGTCATCACTACCATCGGGTACGGCCACGC
Line 3 GTTCCCCGGCTCCTTCTACTTCGCCATCACCGTCATCACTACCATCGGGTACGGCCACGC
370 380 390 400 410 420
FCTR11 CGCGCCGGGTACGGACTCCGGCAAGGTCTTCTGCATGTTCTACGCGCTCCTGGGCATCCC
Line 2 CGCGCCGGGTACGGACTCCGGCAAGGTCTTCTGCATGTTCTACGCGCTCCTGGGCATCCC
Line 3 CGCGCCGGGTACGGACTCCGGCAAGGTCTTCTGCATGTTCTACGCGCTCCTGGGCATCCC
430 440 450 460 470 480
FCTR11 GCTGACGCTGGTCACTTTCCAGAGCCTGGGCGAACGGCTGAACGCGGTGGTGCGGCGCCT
Line 2 GCTGACGCTGGTCACTTTCCAGAGCCTGGGCGAACGGCTGAACGCGGTGGTGCGGCGCCT
Line 3 GCTGACGCTGGTCACTTTCCAGAGCCTGGGCGAACGGCTGAACGCGGTGGTGCGGCGCCT
490 500 510 520 530 540
FCTR11 CCTGTTGGCGGCCAAGTGCTGCCTGGGCCTGCGGTGGACGTGCGTGTCCACGGAGAACCT
Line 2 CCTGTTGGCGGCCAAGTGCTGCCTGGGCCTGCGGTGGACGTGCGTGTCCACGGAGAACCT
Line 3 CCTGTTGGCGGCCAAGTGCTGCCTGGGCCTGCGGTGGACGTGCGTGTCCACGGAGAACCT
550 560 570 580 590 600
FCTR11 GGTGGTGGCCGGGCTGCTGGCGTGTGCCGCCACCCTGGCCCTCGGGGCCGTCGCCTTCTC
Line 2 GGTGGTGGCCGGGCTGCTGGCGTGTGCCGCCACCCTGGCCCTCGGGGCCGTCGCCTTCTC
Line 3 GGTGGTGGCCGGGCTGCTGGCGTGTGCCGCCACCCTGGCCCTCGGGGCCGTCGCCTTCTC
610 620 630 640 650 660
FCTR11 GCACTTCGAGGGCTGGACCTTCTTCCACGCCTACTACTACTGCTTCATCACCCTCACCAC
Line 2 GCACTTCGAGGGCTGGACCTTCTTCCACGCCTACTACTACTGCTTCATCACCCTCACCAC
Line 3 GCACTTCGAGGGCTGGACCTTCTTCCACGCCTACTACTACTGCTTCATCACCCTCACCAC
670 680 690 700 710 720
FCTR11 CATCGGCTTCGGCGACTTCGTGGCACTGCAGAGCGGCGAGGCGCTGCAGAGGAAGCTCCC
Line 2 CATCGGCTTCGGCGACTTCGTGGCACTGCAGAGCGGCGAGGCGCTGCAGAGGAAGCTCCC
Line 3 CATCGGCTTCGGCGACTTCGTGGCACTGCAGAGCGGCGAGGCGCTGCAGAGGAAGCTCCC
730 740 750 760 770 780
FCTR11 CTACGTGGCCTTCAGCTTCCTCTACATCCTCCTGGGGCTCACGGTCATTGGCGCCTTCCT
Line 2 CTACGTGGCCTTCAGCTTCCTCTACATCCTCCTGGGGCTCACGGTCATTGGCGCCTTCCT
Line 3 CTACGTGGCCTTCAGCTTCCTCTACATCCTCCTGGGGCTCACGGTCATTGGCGCCTTCCT
790 800 810 820 830 840
FCTR11 CAACCTGGTGGTCCTGCGCTTCCTCGTTGCCAGCGCCGACTGGCCCGAGCGCGCTGCCCG
Line 2 CAACCTGGTGGTCCTGCGCTTCCTCGTTGCCAGCGCCGACTGGCCCGAGCGCGCTGCCCG
Line 3 CAACCTGGTGGTCCTGCGCTTCCTCGTTGCCAGCGCCGACTGGCCCGAGCGCGCTGCCCG
850 860 870 880 890 900
FCTR11 CACCCCCAGCCCGCGCCCCCCGGGGGCGCCCGAGAGCCGTGGCCTCTGGCTGCCCCGCCG
Line 2 CCCCCCCAGCCCGCGCCCCCCGGGGGCGCCCGAGAGCCGTGGCCTCTGGCTGCCCCGCCG
Line 3 CCCCCCCAGCCCGCGCCCCCCGGGGGCGCCCGAGAGCCGTGGCCTCTGGCTGCCCCGCCG
910 920 930 940 950 960
FCTR11 CCCGGCCCGCTCCGTGGGCTCCGCCTCTGTCTTCTGCCACGTGCACAAGCTGGAGAGGTG



A BlastP search against the FCTR11 protein also identified FCTR11 as having high homology to the potassium channel proteins TASK and KT3.3, as shown in Table 11E. Line 1 shows the FCTR11 polypeptide (SEQ ID NO:22), line 2 is the human TASK protein (gi|10944275| emb|CAC14068.1| (AL118522) dJ781B1.1 (A novel protein similar to the acid sensitive potassium channel protein TASK (KCNK3)) [Homo sapiens])(SEQ ID NO:58), line 3 is the human KT3.3 protein (gi|11228686| gb|AAG33127.1|AF257081_1 (AF257081) two pore potassium channel KT3.3 [Homo sapiens]) (SEQ ID NO:59), and line 4 is the guinea pig TASK3 protein (gi|7546839|gb|AAF63706.1|AF212827_1 (AF212827) potassium channel TASK3 [Cavia porcellus])(SEQ ID NO:60).

Table 11E: BlastP search of FCTR11 protein



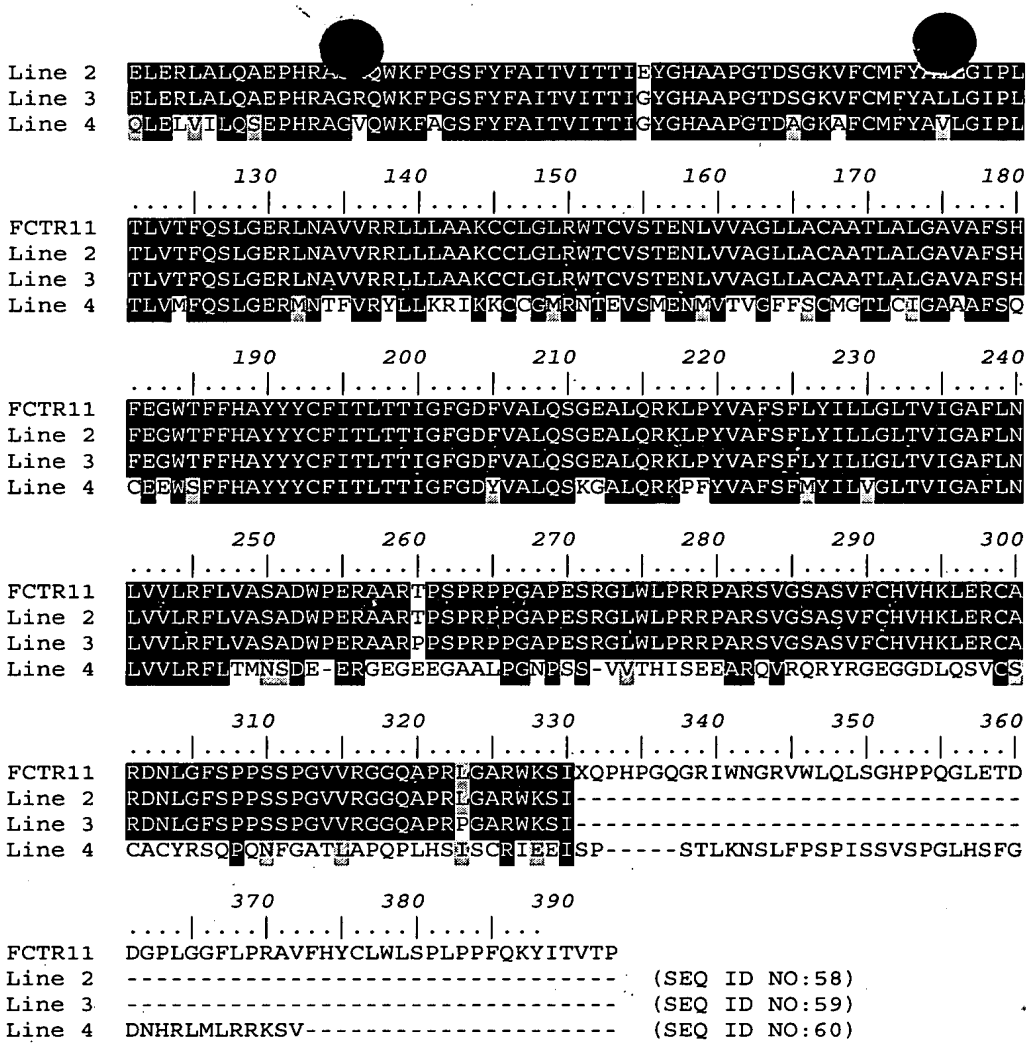


Table 11F. BLASTX of FCTR11 nucleotide with CTBAK.

```
>ptnr:SPTREMBL-ACC:O35111 CTBAK - MUS MUSCULUS (MOUSE), 409 aa.
Score = 832 (292.9 bits), Expect = 1.0e-85, Sum P(2) = 1.0e-85
 Identities = 168/258 (65%), Positives = 200/258 (77%), Frame = +1

Query:     1 MRRPSVRAAGLVLCTLCYLLVGAAVFDALESEAES-GRQRLLVQKRGALRRKFGFSAEDY 177
             |+| +||   |++||  |||||||||||||| |   |||| +++   || ++  |   |
Sbjct:     1 MKRQNVRTLALIVCTFTYLLVGAAVFDALESEPEMIERQRLELRQL-ELRARYNLSEGGY 59

Query:   178 RELERLALQAEPHRAGRQWKFPGSFYFAITVITTIEYGHAAPGTDSGKVFCMFYALLGIP 357
             ||||+ |+ +||+|| ||+| |||||||||||| |||||| || ||||||||||||||
Sbjct:    60 EELERVVLRLKPHKAGVQWRFAGSFYFAITVITTIGYGHAAPSTDGGKVFCMFYALLGIP 119

Query:   358 LTLVTFQSLGERLNAVVRRLLLAAKCCLGLRWTCVSTENLVVAGLLACAATLALGAVAFS 537
             |||| |||||||+|  || ||  ||  ||+|   ||  |+|+ | ++| +|| +|| |||
Sbjct:   120 LTLVMFQSLGERINTFVRYLLLHRAKRGLGMRHAEVSMANMVLIGFVSCISTLCIGAAAFS 179

Query:   538 HFEGWTFFHAYYYCFITLTTIGFGDFVALQSGEALQRKLPYVAFSFLYILLGLTVIGAFL 717
             ++| |||| ||||||||||||||+||||  +||| +  ||||||+||| |||||||||
Sbjct:   180 YYERWTFFQAYYYCFITLTTIGFGDYVALQKDQALQTQPQYVAFSFVYILTGLTVIGAFL 239

Query:   718 NLVVLRFLVASADWPERAA 774
             |||||||+  +|+  +| |
Sbjct:   240 NLVVLRFMTMNAEDEKRDA 258  (SEQ ID NO:61)

 Score = 52 (18.3 bits), Expect = 1.0e-85, Sum P(2) = 1.0e-85
 Identities = 17/35 (48%), Positives = 20/35 (57%), Frame = +2

Query:   941 SCVAGRLPGLGPGGSPSDNPTQAR----VESGMGGSGF 1042
             ||++|    || |  | |  | |     |  |+|||||
```

```
Sbjct:   277 SCLSG---S[redacted]GVRPRDPVTCAAAAGGVGVGVGGSGF 311  (SEQ ID NO:62)

 Score = 40 (14.1 bits), Expect = 1.9e-84, Sum P(2) = 1.9e-84
 Identities = 13/39 (33%), Positives = 16/39 (41%), Frame = +2

Query:   941 SCVAGRLPGLGPGGSPSDNPTQARVESGMGGSGFSYQGT 1057
             +||        | ||  || |+   + ||   |  |   |
Sbjct:   353 TCVEHSHSSPGGGGRYSDTPSHPCLCSGTQRSAISSVST 391  (SEQ ID NO:63)
```

Potassium channels are ubiquitous multisubunit membrane proteins that regulate membrane potential in numerous cell types. One family of mammalian K+ channels is characterized by the presence of 4 transmembrane domains and 2 P domains per subunit; this family includes TASK, TWIK (KCNK1; OMIM 601745) and TREK (KCNK2; OMIM 603219). See, Duprat *et al.*, 1997 *EMBO J.* 16: 5464-5471. The human cDNA, designated TASK, encodes a 394-amino acid polypeptide with 85% identity to the mouse ortholog. See, Duprat *et al.*, 1997. The sequence contains consensus sites for N-linked glycosylation and for phosphorylation at the C-terminal. Northern blot analysis showed that TASK is expressed in a variety of human tissues, with highest levels in pancreas and placenta. See, Duprat *et al.*, 1997. Expression of the TASK cDNA revealed that the functional protein creates currents that are K(+)-selective, instantaneous, and noninactivating. See, OMIM 603220. These currents showed an outward rectification when external K+ was low, but evinced absence of activation and inactivation kinetics as well as voltage independence, characteristics of so-called leak or background conductances. See, OMIM 603220. TASK currents were very sensitive to small changes in extracellular pH, suggesting that TASK has a role in cellular responses to changes in extracellular pH. See, OMIM 603220.

Finally, FCTR11 was found to have high homology to the domains shown in Table 11G.

Table 11G: CD domain analysis of FCTR11

Sequences producing significant alignments:	**Score (bits)**	**E value**
TWIK_channel, TASK K+ channel	284	5e-78
CNG_membrane, Transmembrane region cyclic Nucleotide Gated Cha...	35.8	0.004

The nucleic acids and proteins of the invention are potentially useful in the treatment of cancer, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, and hematopoietic disorders.

FCTR12 (AL121574_A)

The novel nucleic acid encoding a novel protein C-terminal fragment is shown in Table 12A. A TAG stop codon was identified at the 3' end indicating that this sequence is a coding sequence. This sequence originates in clone RP3-441A12 of chromosome 6.

Table 12A. FCTR12 (AL121574_A) nucleotide sequence (SEQ ID NO:23).

natcagactctattgaccgccactctaacgttgtcaggcattgtggcaattgtgtccttgtggctttggg
catttaagcttcactacttgacctctatagttttggcatcttctcatacacatgactatcagcaagctaa
attatttactgactgtcctgctccccgcactccgcctttgaggcgcggaacgaagtggcacgcccggatc
ccagctgatcagcggctgggctttggcgttggctcccccgggcgagaccattgtgactcctcgggagggg
cgcacgccggggagggggcggagcggccattgtccggtcagcgcagcctccgggggagggacggtgtta
cggagacagcagggcccggggcttcagagcggccgctgcgactccggagccggcgggggctccggtcct
tccctgcgccaccgcacaggacatctctctggctggggagcggcggtgagacccgccgagggcgtctgtg
tccctcctcccccgcggtcctcgagcggggcccgggcccagccgccgccaccgctgccgccgccgagctc
cgccgccgccgagcaccatgggagacgctgggagcgagcgcagcaaagcgcccagcctgccgcctcgctg
tccctgcggcttctggggactaacggcagttcctttaggattgctgctctttcgagtgacttaggctgca
ggacttgctgcccagcattgcccagtcaggacactaatcagtgtggctcggttgaa**tag**

The encoded C-terminal fragment of the encoded protein is presented using the one-letter code in Table 12B. The C-terminal fragment disclosed has a very high probability of being sorted to the plasma membrane. No cleavage site for a signal peptide was detected.

Table 12B. Encoded FCTR12 protein sequence (SEQ ID NO:24).

XQTLLTATLTLSGIVAIVSLWLWAFKLHYLTSIVLASSHTHDYQQAKLFTDCPAPRTPPLRRGTKWHARI
PADQRLGFGVGSPGRDHCDSSGGAHAGEGAERPLSGQRSLRGRGRCYGDSRARGFRAAAATPEPAGGSGP
SLRHRTGHLSGWGAAVRPAEGVCVPPPPRSSSGARAQPPPPLPPPSSAAAEHHGRRWERAQQSAQPAASL
SLRLLGTNGSSFRIAALSSDLGCRTCCPALPSQDTNQCGSVE

In a search of sequence databases, no similarities were found to any known nucleic acid or protein.

The nucleic acids and proteins of the invention are potentially useful in the treatment of cancer, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, and hematopoietic disorders.

FCTR13 (AL121723_A)

A novel nucleic acid encoding a novel secreted morphogenic protein is shown in Table 13A. It was identified in chromosome 20 clone RP5-854E16. An initiation codon is shown at the beginning of the sequence and a TGA stop codon was identified at the 3' end indicating that this sequence is a coding sequence. These are shown in bold face in Figure 13A.

Table 13A. Nucleotide sequence (SEQ ID NO:25) of FCTR13 (AL121723_A).

atgcggcatccgctggtcctgctgctgctcctctctgccctggtgacctccttcactgcagcctctatcc
acgatgctcatgcccaagagagctccttgggtcttacaggcctccagagcctactccaaggcttcagccg
acttttcctgaaagatgacctgcttcggggcatagacagcttcttctctgcccccatggacttccggggc
ctccctaggaactaccaacaagaggagaacgaggagcaccagctgaggaacaacaccctctccagccacc
tccatattgacaaggtgaccgacaataagacaggagaggtgctgatctccgagaaggtggtggcatccat
ccagccggcggaggggagcttcgagggtaactggaaggcggcggccctggtgtccatccggaaggctatg
gacaacttccatgcagagctccatccccgggtggccttttggatcatgaagctgccacggtggaggtccc
accacaatgtcctggagggcggccgctggctcagtgagaagcgacaccgcctgcaggccatccaggatgg
gctccacgaggggacccgcgaggacgtcctaaaagaggggacccagggctcctcccactccgggctgtcc
tccgaaagacccacttactgtacatcttcaggctttcctggcagctataggggttgggaccggggagcac
ctgcaagctgggttggtgtctgggtcagcgtatcaaagggcctggcacatggacccacagggttgggcct
ggagcctggatccagtgggatagactttgtgaatgcgttcatggagggctacagtaaccaaaacatcatg

gtactagtacaaaaacgg[redacted]acatagaccaatgcaacagaacagagaggc[redacted]agaaataaggccacacacc
tacaaccatctgatcttcgacaaagc**tga**

The encoded protein is presented using the one-letter code in Table 13B. The protein has a very high probability of secreted extracellularly. Cleavage of a signal peptide is predicted to occur between residues 28 and 29, *i.e.* at the dash in the sequence AHA-QES.

Table 13B. Encoded FCTR13 protein sequence (SEQ ID NO:26).

MRHPLVLLLLLSALVTSFTAASIHDAHAQESSLGLTGLQSLLQGFSRLFLKDDLLRGIDSFFSAPMDFRG
LPRNYQQEENEEHQLRNNTLSSHLHIDKVTDNKTGEVLISEKVVASIQPAEGSFEGNWKAAALVSIRKAM
DNFHAELHPRVAFWIMKLPRWRSHHNVLEGGRWLSEKRHRLQAIQDGLHEGTREDVLKEGTQGSSHSGLS
SERPTYCTSSGFPGSYRGWDRGAPASWVGVWVSVSKGLAHGPTGLGLEPGSSGIDFVNAFMEGYSNQNIM
VLVQKRIHRPMQQNREARNKATHLQPSDLRQS

In a search of sequence databases, it was found, for example, that the nucleic acid sequence has 356 of 388 bases (91%) identical to human cysteine-rich secreted protein-like-N cDNA (patn: : V07910) (Table 13C). The full amino acid sequence of the protein was found to have 166 of 218 residues (76%), identical to, and 181 of 218 residues (83%) positive with, human dickkopf-1 (dkk-1) having a total of 242 amino acid residues. This protein (soggy-1 protein) is a member of a novel family of secreted proteins and functions in head induction during *Xenopus* embryogenesis, acting as a potent inhibitor of Wnt signaling. (TREMBLNEW-ACC:AAF02678) (Table 13D).

Table 13C. BLASTN of FCTR13 with GenBank V07910

```
>patn:V07910 Human cysteine-rich secreted protein-like-N cDNA - Homo sapiens, 928 bp.
Score = 1652 (247.9 bits), Expect = 1.6e-123, Sum P(2) = 1.6e-123
 Identities = 356/388 (91%), Positives = 356/388 (91%), Strand = Plus / Plus

Query:     1 ATGCGGCATCCGCTGGTCCTGCTGCTGCTCCTCTCTGCCCTGGTGACCTCCTTCACTGCA 60
             | ||||||||  |||||||||||||||||||||||||  |||||||||  | |||  | |||||
Sbjct:   105 AGGCGGCATCTGCTGGTCCTGCTGCTGCTCCTCTCTACCCTGGTGATCCCCTCCGCTGCA 164

Query:    61 GCCTCTATCCACGATGCTCATGCCCAAGAGAGCTCCTTGGGTCTTACAGGCCTCCAGAGC 120
             ||  |||||||  ||||||  | ||||||||||||||||||||||  ||||||||||||||
Sbjct:   165 GCTCCTATCCATGATGCTGACGCCCAAGAGAGCTCCTTGGGTCTCACAGGCCTCCAGAGC 224

Query:   121 CTACTCCAAGGCTTCAGCCGACTTTTCCTGAAAGATGACCTGCTTCGGGGCATAGACAGC 180
             |||||||||||||||||||||||||||||||||  | ||||||||||||||||||||||
Sbjct:   225 CTACTCCAAGGCTTCAGCCGACTTTTCCTGAAAGGTAACCTGCTTCGGGGCATAGACAGC 284

Query:   181 TTCTTCTCTGCCCCCATGGACTTCCGGGGCCTCCCTAGGAACTACCAACAAGAGGAGAAC 240
             ||  |||||||||||||||||||||||||||||||||  |||||||||  ||||||||||
Sbjct:   285 TTATTCTCTGCCCCCATGGACTTCCGGGGCCTCCCTGGGAACTACCACAAAGAGGAGAAC 344

Query:   241 GAGGAGCACCAGCTGAGGAACAACACCCTCTCCAGCCACCTCCATATTGACAAGGTGACC 300
             |||||||||||||| ||||||||||||||||||||||||||  || ||||||  |||||
Sbjct:   345 CAGGAGCACCAGCTGGGGAACAACACCCTCTCCAGCCACCTCCAGATCGACAAGATGACC 404

Query:   301 GACAATAAGACAGGAGAGGTGCTGATCTCCGAGAAGGTGGTGGCATCCATCCAGCCGGCG 360
             |||||  |||||||||||||||||||||||||||  ||||||||||||  ||  ||  |||
Sbjct:   405 GACAACAAGACAGGAGAGGTGCTGATCTCCGAGAATGTGGTGGCATCCATTCAACCAGCG 464

Query:   361 GAGGGGAGCTTCGAGGGTAACTGGAAGG 388
             ||||||||||||||||  |  | |||||
Sbjct:   465 GAGGGGAGCTTCGAGGGTGATTTGAAGG 492  (SEQ ID NO:64)
```

```
 Score = 1244 (186.7 bits), Expect = 1.6e-123, Sum P(2) = 1.6e-123
 Identities = 282/322 (87%), Positives = 282/322 (87%), Strand = Plus / Plus

Query:   384 GAAGGCGGCGGCCCTGGTGTCCATCCGGAAGGCTATGGACAACTTCCATGCAGAGCTCCA 443
             | ||  || |||||||||  |||||| |||||| | ||||| ||||||  |||| |||||
Sbjct:   506 GGAGAAGGAGGCCCTGGTACCCATCCAGAAGGCCACGGACAGCTTCCACACAGAACTCCA 565

Query:   444 TCCCCGGGTGGCCTTTTGGATCATGAAGCTGCCACGGTGGAGGTCCCACCACAATGTCCT 503
             ||||||||||||||| |||||||| |||||||||||| |||||||||||||  ||| |||
Sbjct:   566 TCCCCGGGTGGCCTTCTGGATCATTAAGCTGCCACGGCGGAGGTCCCACCAGGATGCCCT 625

Query:   504 GGAGGGCGGCCGCTGGCTCAGTGAGAAGCGACACCGCCTGCAGGCCATCCAGGATGGGCT 563
             |||||||||||| ||||||||| |||||||||||||||||||||||||||| ||||||  ||
Sbjct:   626 GGAGGGCGGCCACTGGCTCAGCGAGAAGCGACACCGCCTGCAGGCCATCCGGGATGGACT 685

Query:   564 CCACGAGGGGACCCGCGAGGACGTCCTAAAAGAGGGGACCCAGGGCTCCTCCCACTCCGG 623
             ||  | |||||||||  | |||||||||| |||||||||| ||  |||||||||||||  |
Sbjct:   686 CCGCAAGGGGACCCACAAGGACGTCCTAGAAGAGGGGACCGAGAGCTCCTCCCACTCCAG 745

Query:   624 GCTGTCCTCC-GAAAGACCCACTTACTGTACATCTTCAGGCTTTCCTGGCAGCTATAGGG 682
             ||||||| || |||||||||||||||||||||||| ||||||  ||  ||||||| |||||
Sbjct:   746 GCTGTCCCCCCGAAAGACCCACTTACTGTACATCCTCAGGCCCTCTCGGCAGCTGTAGGG 805

Query:   683 GTTGGGACCGGGGGAGCACCTGC 704
             || ||||||||||||||||||||
Sbjct:   806 GTGGGGACCGGGGGAGCACCTGC 827  (SEQ ID NO:65)
```

Table 13D. BLASTX of FCTR13 with Soggy-1.

```
>ptnr:TREMBLNEW-ACC:AAF02678 SOGGY-1 PROTEIN - Homo sapiens (Human), 242 aa. Dickkopf-
1 (dkk-1) is member of a novel family of secreted proteins and functions in head
induction during Xenopus embryogenesis, acting as a potent inhibitor of Wnt signaling.
 Score = 813 (286.2 bits), Expect = 6.3e-84, Sum P(2) = 6.3e-84
 Identities = 166/218 (76%), Positives = 181/218 (83%), Frame = +1

Query:     4 RHPLVLLLLLLSALVTSFTAASIHDAHAQESSLGLTGLQSLLQGFSRLFLKDDLLRGIDSF 183
             || |||||||| ||    || |||| |||||||||||||||||||||| +|||||||
Sbjct:    12 RHLLVLLLLLLSTLVIPSAAAPIHDADAQESSLGLTGLQSLLQGFSRLFLKGNLLRGIDSL 71

Query:   184 FSAPMDFRGLPRNYQQEENEEHQLRNNTLSSHLHIDKVTDNKTGEVLISEKVVASIQPAE 363
             |||||||||| || +|||+|||| |||||||| |||+|||||||||||| |||||||||
Sbjct:    72 FSAPMDFRGLPGNYHKEENQEHQLGNNTLSSHLQIDKMTDNKTGEVLISENVVASIQPAE 131

Query:   364 GSFEGNWKAA------ALVSIRKAMDNFHAELHPRVAFWIMKLPRWRSHHNVLEGGRWLS 525
             |||||+ |         ||| |+|| |+|| ||||||||||+|||| ||| + |||| |||
Sbjct:   132 GSFEGDLKVPRMEEKEALVPIQKATDSFHTELHPRVAFWIIKLPRRRSHQDALEGGHWLS 191

Query:   526 EKRHRLQAIQDGLHEGTREDVLKEGTQGSSHSGLSSER 639
             |||||||||+||| +|| +|||+|||+ |||| ||  +
Sbjct:   192 EKRHRLQAIRDGLRKGTHKDVLEEGTESSSHSRLSPRK 229  (SEQ ID NO:66)


 Score = 54 (19.0 bits), Expect = 6.3e-84, Sum P(2) = 6.3e-84
 Identities = 12/15 (80%), Positives = 12/15 (80%), Frame = +3

Query:   633 RKTHLLYIFRLSWQL 677
             |||||||| | | ||
Sbjct:   228 RKTHLLYILRPSRQL 242  (SEQ ID NO:67)
```

A multiple sequence alignment for FCTR13 AL121723_A A is given in Table 13E in a ClustalW analysis comparing the protein of the invention with related protein sequences. The FCTR13 polypeptide is shown on line 1, the human Soggy-1 protein (gi|7657554| ref| NP_055234.1| soggy-1 gene [Homo sapiens])(SEQ ID NO:68) on line 2, mouse Soggy-1 protein

(gi|10644567| gb|AAG21340.1| AF274312_1 (AF274312) soggy precursor [Mus musculus]) (SEQ ID NO:69) on line 3, and mouse Soggy-1 protein (gi|10644569| gb|AAG21341.1| AF274313_1 (AF274313) soggy precursor [Mus musculus]) (SEQ ID NO:70) on line 4. Table 13E depicts a ClustalW alignment of FCTR13 against proteins from a public database. Based on this alignment, black outlined amino acid residues indicate regions of conserved sequence (i.e., regions that may be required to preserve structural or functional properties); grayed amino acid residues can be mutated to a residue with comparable steric and/or chemical properties without altering protein structure or function (e.g. L to V, I, or M); non-highlighted amino acid residues can potentially be mutated to a much broader extent without altering structure or function.

Table 13E. ClustalW alignment of the FCTR13.

```
10         20         30         40         50         60
           |          |          |          |          |          |
FCTR13     ----------MRHPLVLLLLLSALVTSFIAASIHDAHAQESSLGLTGLQSLLQGFSRLFL
Line 2     MGEASPPAPARRHLLVLLLLLSTLVIPSAAAPIHDADAQESSLGLTGLQSLLQGFSRLFL
Line 3     ----------MCRLRVLLLLLPLAFVSSSALPIHDVDSQQNTSGFLGLQRLLQSFSRLFL
Line 4     ----------MCRLRVLLLLLPLAFVSSSALPIHDVDSQQNTSGFLGLQRLLQSFSRLFL

                70         80         90         100        110        120
           |          |          |          |          |          |          |
FCTR13     KDDLLRGIDSFFSAPMDFRGLPRNYQQEENEEHQLRNNTLSSHLHIDKVTDNKTGEVLIS
Line 2     KGNLLRGIDSLFSAPMDFRGLPGNYHKEENQEHQLGNNTLSSHLQIDKMTDNKTGEVLIS
Line 3     KNDLLRDLDNFFSSPMDFRDLPRNFHQEENQEHRMGNHTLSSHLQIDKVTDNQTGEVLIS
Line 4     KNDLLRDLDNFFSSPMDFRDLPRNFHQEENQEHRMGNHTLSSHLQIDKVTDNQTGEVLIS

                130        140        150        160        170        180
           |          |          |          |          |          |          |
FCTR13     EKVVASIQPAEGSFEGNWKAA------ALVSIRKAMDNFHAELHPRVAFWIMKLPRWRSH
Line 2     ENVVASIQPAEGSFEGDLKVPRMEEKEALVPIQKATDSFHTELHPRVAFWIIKLPRRRSH
Line 3     EKVEASIEPER-NPEGDWKVPKVEAKEPPVPVQKVTDSLHPEPR-QVAFWIMKMPRRRTQ
Line 4     EKVEASIEPER-NPEGDWK-----------------------------------------

                190        200        210        220        230        240
           |          |          |          |          |          |          |
FCTR13     HNVLEGGRWLSEKRHRLQAIQDGLHEGTREDVLKEGTQGSSHSGLSSERPTYCTSSGFPG
Line 2     QDALEGGHWLSEKRHRLQAIRDGLRKGTHKDVLEEGTESSSHSRLSPRK----------
Line 3     PDVQDGGRWLIEKRHRMQAIRDGLRGGAREDSLEDGVHIPQHAKLPVRK----------
Line 4     ------------------------------------------------------------

                250        260        270        280        290        300
           |          |          |          |          |          |          |
FCTR13     SYRGWDRGAPASWVGVWVSVSKGLAHGPTGLGLEPGSSGIDFVNAFMEGYSNQNIMVLVQ
Line 2     ------------------------------------------------------------
Line 3     ------------------------------------------------------------
Line 4     ------------------------------------------------------------

                310        320
           |          |          |
FCTR13     KRIHRPMQQNREARNKATHLQPSDLRQS   (SEQ ID NO:26)
Line 2     ------------THLLYILRPS--RQL   (SEQ ID NO:68)
Line 3     ------------THFLYILRPS--QQL   (SEQ ID NO:69)
Line 4     ----------------------------   (SEQ ID NO:70)
```

From these analyses, it is seen that the FCTR13 AL121723_A A nucleic acid and protein have a strong similarity with human soggy-1 protein.

The nucleic acids and proteins of the invention are potentially useful in the treatment of cancer, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, and hematopoietic disorders.

FCTR14 (AL121756_A)

The novel nucleic acid encoding a novel secreted protein is shown in Table 14A. This sequence contains an initiation codon at the 5' end, and a TGA stop codon was identified at the 3' end indicating that this sequence is a coding sequence. The start and stop codons are shown in bold type. This sequence originates in chromosome 20 clone RP4-726C3.

Table 14A. FCTR14 (AL121756_A) nucleotide sequence (SEQ ID NO:27).

```
atgctgcggatcctgtgcctggcactctgcagcctgctgactggcacgcgagctgaccctggggcactgc
tgcggttgggcatggacatcatgaaccgtgaggtccagagcgccatggatgagagtcatatcctggagaa
gatggcagccgaggcaggcaagaaacagccagggatgaaacctatcaagggcatcaccaatttgaaggtg
aaggatgtccagctgcccgtcatcacactgaactttgtacctggagtgggcatcttccaatgtgtgtcca
caggcatgaccgtcactggcaagagcttcatgggagggaacatggagatcatcgtggccctgaacatcac
agccaccaaccggcttctgcgggatgaggagacaggcctccccgtgttcaagagtgagggctgtgaggtc
atcctggtcaatgtgaagactaacctgcctagcaacatgctccccaagatggtcaacaagttcctggaca
gcaccctgcacaaagtcctccctgggctgatgtgtcccgccatcgatgcagtcctggtgtatgtgaacag
gaagtggaccaacctcagtgaccccatgcctgtgggccagatgggcaccgtcaaatatgttctgatgtcc
gcaccagccaccacagccagctacatccaactggacttcagtcctgtggtgcagcagcaaaagggcaaaa
ccatcaagcttgctgatgccggggaggccctcacgttccctgagggttatgccaaaggctcgtcgcagct
gctgctcccagccaccttcctctctgcagagcttgcccttctgcagaagtcctttcatgtgaatatccag
gatacaatgattggtgagctgcccccacaaaccaccaagaccctggctcgcttcattcctgaagtggctg
tagcttatcccaagtcaaagcccttgacgacccagatcaagataaagaagcctcccaaggtcactatgaa
gacaggcaagagcctgctgcacctccacagcaccctggagatgttcgcagctcggtggcggagcaaggct
ccaatgtccctctttctcctagaagtgcacttcaatctgaaggtccagtactcagtgcatgagaaccagc
tgcagatggccacttctttggacagattactgagcttgtcccggaagtcctcatcgattggcaacttcaa
tgagagggaattaactggcttcatcaccagctatctcgaagaagcctacatcccagttgtcaatgatgtg
cttcaagtggggctcccactcccggactttctggccatgaattacaacctggctgagctggacatagtag
agcttgggggcatcatggaacctgccgacatatga
```

The encoded protein is presented using the one-letter code in Table 14B. The protein has a moderate probability of being sorted to the plasma membrane. A signal peptide most likely is cleaved between residues 18 and 19, *i.e.*, at the dash in the amino acid sequence TRA-DPG.

Table 14B. Encoded FCTR14 protein sequence (SEQ ID NO:28).

```
MLRILCLALCSLLTGTRADPGALLRLGMDIMNREVQSAMDESHILEKMAAEAGKKQPGMKPIKGITNLKV
KDVQLPVITLNFVPGVGIFQCVSTGMTVTGKSFMGGNMEIIVALNITATNRLLRDEETGLPVFKSEGCEV
ILVNVKTNLPSNMLPKMVNKFLDSTLHKVLPGLMCPAIDAVLVYVNRKWTNLSDPMPVGQMGTVKYVLMS
APATTASYIQLDFSPVVQQQKGKTIKLADAGEALTFPEGYAKGSSQLLLPATFLSAELALLQKSFHVNIQ
DTMIGELPPQTTKTLARFIPEVAVAYPKSKPLTTQIKIKKPPKVTMKTGKSLLHLHSTLEMFAARWRSKA
PMSLFLLEVHFNLKVQYSVHENQLQMATSLDRLLSLSRKSSSIGNFNERELTGFITSYLEEAYIPVVNDV
LQVGLPLPDFLAMNYNLAELDIVELGGIMEPADI
```

A BLASTN search of sequence databases for the FCTR14 nucleic acid sequence identified significant similarities to the human genomic clone HSDJ726C3, isolated from human DNA sequence from clone RP4-726C3 on chromosome 20. In a BLASTX comparison, it was

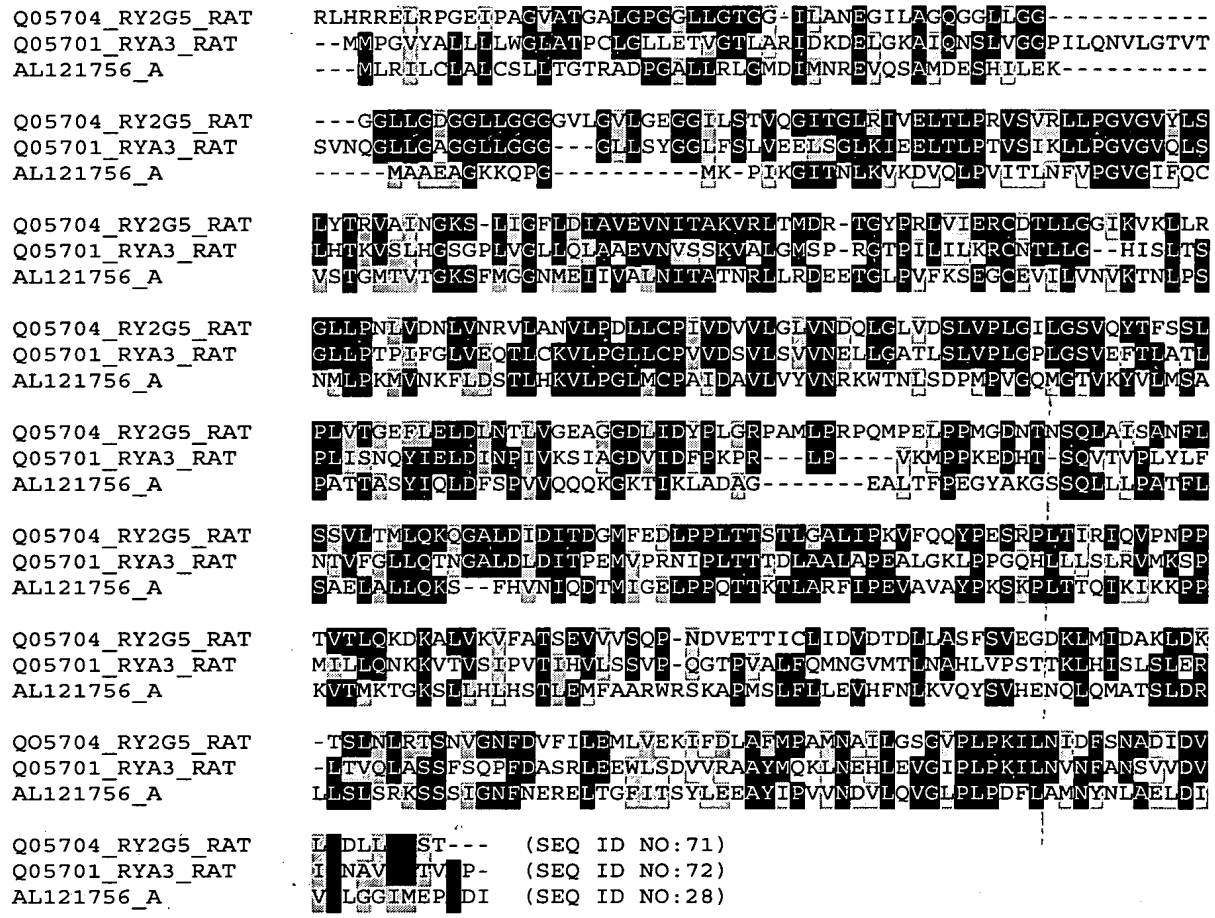
found that the full FCTR14 amino acid sequence has 130 of 391 residues (33%), are identical to, and 229 of 391 residues (58%) positive with, rat potential ligand-binding protein RY2G5 having a total of 409 amino acid residues (SPTREMBL-ACC:Q05704) (SEQ ID NO:71). The BLASTX alignment is shown in Table 14C.

Table 14C. BLASTX alignment of FCTR14

```
>ptnr:SPTREMBL-ACC:Q05704 POTENTIAL LIGAND-BINDING PROTEIN RY2G5 - RATTUS NORVEGICUS
(RAT), 470 aa          (fragment).
CC   -!- TISSUE SPECIFICITY: SUBREGIONS OF THE OLFACTORY MUCOSA.

Score = 579 (203.8 bits), Expect = 2.0e-55, P = 2.0e-55
 Identities = 130/391 (33%), Positives = 229/391 (58%), Frame = +1

Query:   175 MKPIKGITNLKVKDVQLPVITLNFVPGVGIFQCVSTGMTVTGKSFMGGNMEIIVALNITA 354
             +  ++|||  |++ ++  ||  +++   +||||++   +  |  +  +  |||  +|   ++|  |  +||||
Sbjct:    73 LSTVQGITGLRIVELTLPRVSVRLLPGVGVYLSLYTRVAINGKSLIGF-LDIAVEVNITA 131

Query:   355 TNRLLRDEETGLPVFKSEGCEVILVNVKTNLPSNMLPKMVNKFLDSTLHKVLPGLMCPAI 534
               ||   |  || |     | |+ +|   +|   |    +|| +|+  ++   |   ||| L+|| +
Sbjct:    132 KVRLTMDR-TGYPRLVIERCDTLLGGIKVKLLRGLLPNLVDNLVNRVLANVLPDLLCPIV 190

Query:   535 DAVLVYVNRKWTNLSDPMPVGQMGTVKYVLMSAPATTASYIQLDFSPVVQQQKGKTIKLA 714
               | ||   || +    +    +|+| +|+|+|    | |   |  +++|| + +| +   |   |
Sbjct:    191 DVVLGLVNDQLGLVDSLVPLGILGSVQYTFSSLPLVTGEFLELDLNTLVGEAGGDLIDYP 250

Query:   715 DAGEALT----FPEGYAKG---SSQLLLPATFLSAELALLQK--SFHVNIQDTMIGELPP 867
                 |+       ||     |   +|||  + |  |||+  | +|||   +  ++|  | |   +|||
Sbjct:    251 LGRPAMLPRPQMPELPPMGDNTNSQLAISANFLSSVLTMLQKQGALDIDITDGMFEDLPP 310

Query:   868 QTTKTLARFIPEVAVAYPKSKPLTTQIKIKKPPKVTMKTGKSLLHLHSTLEMFAARWRSK 1047
               || ||    ||+|    ||+|+|||  +|++   ||  ||++   |+|+ + +|  |+  ++  +
Sbjct:    311 LTTSTLGALIPKVFQQYPESRPLTIRIQVPNPPTVTLQKDKALVKVFATSEVVVSQ-PND 369

Query:  1048 APMSLFLLEVHFNLKVQYSVHENQLQMATSLDRLLSLSRKSSSIGNFNERELTGFITSYL 1227
                ++ |++|   +|    +||   ++|  +    ||+   ||+ ++|++|||+    |    +
Sbjct:    370 VETTICLIDVDTDLLASFSVEGDKLMIDAKLDKT-SLNLRTSNVGNFDVFILEMLVEKIF 428

Query:  1228 EEAYIPVVNDVLQVGLPLPDFLAMNYNLAELDIVE 1332
               + |++| +|  +|   |+|||   | ++++ |++|++|
Sbjct:    429 DLAFMPAMNAILGSGVPLPKILNIDFSNADIDVLE 463
```

A multiple sequence alignment for FCTR14 AL121756_A is given in Table 14D, with the protein of the invention being shown on line 3, in a ClustalW analysis comparing the protein of the invention with related protein sequences. Table 14D depicts a ClustalW alignment of FCTR13 with proteins from the public database. The alignment is presented against Q05704 - POTENTIAL LIGAND-BINDING PROTEIN RY2G5 (FRAGMENT) (SEQ ID NO:71) and Q05701 - POTENTIAL LIGAND-BINDING PROTEIN RYA3 (SEQ ID NO:72). Based on this alignment, black outlined amino acid residues indicate regions of conserved sequence (i.e., regions that may be required to preserve structural or functional properties); grayed amino acid residues can be mutated to a residue with comparable steric and/or chemical properties without altering protein structure or function (e.g. L to V, I, or M); non-highlighted amino acid residues can potentially be mutated to a much broader extent without altering structure or function.

TABLE 14D ClustalW alignment of FCTR14 (AL121756_A) protein



Finally, FCTR14 was found to have high homology to the domains shown in Table 14D.

Table 14D: CD domain analysis of FCTR14

Sequences producing significant alignments:	Score (bits)	E value
BPI/LBP/CETP C-terminal domain; Bactericidal permeability-incr...	72.8	4e-14
BPI/LBP/CETP N-terminal domain; Bactericidal permeability-incr...	60.8	1e-10
LBP_BPI_CETP, LBP / BPI / CETP family	45.8	5e-06

The FCTR14 nucleic acids and proteins of the invention are potentially useful in the treatment of cancer, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, and hematopoietic disorders.

FCTRX Nucleic Acids and Polypeptides

One aspect of the invention pertains to isolated nucleic acid molecules that encode FCTRX polypeptides or biologically-active portions thereof. Also included in the invention are nucleic acid fragments sufficient for use as hybridization probes to identify FCTRX-encoding nucleic acids (*e.g.*, FCTRX mRNAs) and fragments for use as PCR primers for the amplification

and/or mutation of FCTRX nucleic acid molecules. As used herein, the term "nucleic acid molecule" is intended to include DNA molecules (*e.g.*, cDNA or genomic DNA), RNA molecules (*e.g.*, mRNA), analogs of the DNA or RNA generated using nucleotide analogs, and derivatives, fragments and homologs thereof. The nucleic acid molecule may be single-stranded or double-stranded, but preferably is comprised double-stranded DNA.

An FCTRX nucleic acid can encode a mature FCTRX polypeptide. As used herein, a "mature" form of a polypeptide or protein disclosed in the present invention is the product of a naturally occurring polypeptide or precursor form or proprotein. The naturally occurring polypeptide, precursor or proprotein includes, by way of nonlimiting example, the full length gene product, encoded by the corresponding gene. Alternatively, it may be defined as the polypeptide, precursor or proprotein encoded by an open reading frame described herein. The product "mature" form arises, again by way of nonlimiting example, as a result of one or more naturally occurring processing steps as they may take place within the cell, or host cell, in which the gene product arises. Examples of such processing steps leading to a "mature" form of a polypeptide or protein include the cleavage of the N-terminal methionine residue encoded by the initiation codon of an open reading frame, or the proteolytic cleavage of a signal peptide or leader sequence. Thus a mature form arising from a precursor polypeptide or protein that has residues 1 to N, where residue 1 is the N-terminal methionine, would have residues 2 through N remaining after removal of the N-terminal methionine. Alternatively, a mature form arising from a precursor polypeptide or protein having residues 1 to N, in which an N-terminal signal sequence from residue 1 to residue M is cleaved, would have the residues from residue M+1 to residue N remaining. Further as used herein, a "mature" form of a polypeptide or protein may arise from a step of post-translational modification other than a proteolytic cleavage event. Such additional processes include, by way of non-limiting example, glycosylation, myristoylation or phosphorylation. In general, a mature polypeptide or protein may result from the operation of only one of these processes, or a combination of any of them.

The term "probes", as utilized herein, refers to nucleic acid sequences of variable length, preferably between at least about 10 nucleotides (nt), 100 nt, or as many as approximately, *e.g.*, 6,000 nt, depending upon the specific use. Probes are used in the detection of identical, similar, or complementary nucleic acid sequences. Longer length probes are generally obtained from a natural or recombinant source, are highly specific, and much slower to hybridize than shorter-length oligomer probes. Probes may be single- or double-stranded and designed to have specificity in PCR, membrane-based hybridization technologies, or ELISA-like technologies.

The term "isolated" nucleic acid molecule, as utilized herein, is one which is separated from other nucleic acid molecules which are present in the natural source of the nucleic acid.

Preferably, an "isolated" nucleic acid is free of sequences which naturally flank the nucleic acid (*i.e.*, sequences located at the 5'- and 3'-termini of the nucleic acid) in the genomic DNA of the organism from which the nucleic acid is derived. For example, in various embodiments, the isolated FCTRX nucleic acid molecules can contain less than about 5 kb, 4 kb, 3 kb, 2 kb, 1 kb, 0.5 kb or 0.1 kb of nucleotide sequences which naturally flank the nucleic acid molecule in genomic DNA of the cell/tissue from which the nucleic acid is derived (*e.g.*, brain, heart, liver, spleen, etc.). Moreover, an "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material or culture medium when produced by recombinant techniques, or of chemical precursors or other chemicals when chemically synthesized.

A nucleic acid molecule of the invention, *e.g.*, a nucleic acid molecule having the nucleotide sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29, or a complement of this aforementioned nucleotide sequence, can be isolated using standard molecular biology techniques and the sequence information provided herein. Using all or a portion of the nucleic acid sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29 as a hybridization probe, FCTRX molecules can be isolated using standard hybridization and cloning techniques (*e.g.*, as described in Sambrook, *et al.*, (eds.), MOLECULAR CLONING: A LABORATORY MANUAL 2nd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989; and Ausubel, *et al.*, (eds.), CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, New York, NY, 1993.)

A nucleic acid of the invention can be amplified using cDNA, mRNA or alternatively, genomic DNA, as a template and appropriate oligonucleotide primers according to standard PCR amplification techniques. The nucleic acid so amplified can be cloned into an appropriate vector and characterized by DNA sequence analysis. Furthermore, oligonucleotides corresponding to FCTRX nucleotide sequences can be prepared by standard synthetic techniques, *e.g.*, using an automated DNA synthesizer.

As used herein, the term "oligonucleotide" refers to a series of linked nucleotide residues, which oligonucleotide has a sufficient number of nucleotide bases to be used in a PCR reaction. A short oligonucleotide sequence may be based on, or designed from, a genomic or cDNA sequence and is used to amplify, confirm, or reveal the presence of an identical, similar or complementary DNA or RNA in a particular cell or tissue. Oligonucleotides comprise portions of a nucleic acid sequence having about 10 nt, 50 nt, or 100 nt in length, preferably about 15 nt to 30 nt in length. In one embodiment of the invention, an oligonucleotide comprising a nucleic acid molecule less than 100 nt in length would further comprise at least 6 contiguous nucleotides of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29, or

a complement thereof. Oligonucleotides may be chemically synthesized and may also be used as probes.

In another embodiment, an isolated nucleic acid molecule of the invention comprises a nucleic acid molecule that is a complement of the nucleotide sequence shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29, or a portion of this nucleotide sequence (*e.g.*, a fragment that can be used as a probe or primer or a fragment encoding a biologically-active portion of an FCTRX polypeptide). A nucleic acid molecule that is complementary to the nucleotide sequence shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29, is one that is sufficiently complementary to the nucleotide sequence shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29, that it can hydrogen bond with little or no mismatches to the nucleotide sequence shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29, thereby forming a stable duplex.

As used herein, the term "complementary" refers to Watson-Crick or Hoogsteen base pairing between nucleotides units of a nucleic acid molecule, and the term "binding" means the physical or chemical interaction between two polypeptides or compounds or associated polypeptides or compounds or combinations thereof. Binding includes ionic, non-ionic, van der Waals, hydrophobic interactions, and the like. A physical interaction can be either direct or indirect. Indirect interactions may be through or due to the effects of another polypeptide or compound. Direct binding refers to interactions that do not take place through, or due to, the effect of another polypeptide or compound, but instead are without other substantial chemical intermediates.

Fragments provided herein are defined as sequences of at least 6 (contiguous) nucleic acids or at least 4 (contiguous) amino acids, a length sufficient to allow for specific hybridization in the case of nucleic acids or for specific recognition of an epitope in the case of amino acids, respectively, and are at most some portion less than a full length sequence. Fragments may be derived from any contiguous portion of a nucleic acid or amino acid sequence of choice. Derivatives are nucleic acid sequences or amino acid sequences formed from the native compounds either directly or by modification or partial substitution. Analogs are nucleic acid sequences or amino acid sequences that have a structure similar to, but not identical to, the native compound but differs from it in respect to certain components or side chains. Analogs may be synthetic or from a different evolutionary origin and may have a similar or opposite metabolic activity compared to wild type. Homologs are nucleic acid sequences or amino acid sequences of a particular gene that are derived from different species.

Derivatives and analogs may be full length or other than full length, if the derivative or analog contains a modified nucleic acid or amino acid, as described below. Derivatives or

analogs of the nucleic acids or proteins of the invention include, but are not limited to, molecules comprising regions that are substantially homologous to the nucleic acids or proteins of the invention, in various embodiments, by at least about 70%, 80%, or 95% identity (with a preferred identity of 80-95%) over a nucleic acid or amino acid sequence of identical size or when compared to an aligned sequence in which the alignment is done by a computer homology program known in the art, or whose encoding nucleic acid is capable of hybridizing to the complement of a sequence encoding the aforementioned proteins under stringent, moderately stringent, or low stringent conditions. See *e.g.* Ausubel, *et al.*, CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, New York, NY, 1993, and below.

A "homologous nucleic acid sequence" or "homologous amino acid sequence," or variations thereof, refer to sequences characterized by a homology at the nucleotide level or amino acid level as discussed above. Homologous nucleotide sequences encode those sequences coding for isoforms of FCTRX polypeptides. Isoforms can be expressed in different tissues of the same organism as a result of, for example, alternative splicing of RNA. Alternatively, isoforms can be encoded by different genes. In the invention, homologous nucleotide sequences include nucleotide sequences encoding for an FCTRX polypeptide of species other than humans, including, but not limited to: vertebrates, and thus can include, *e.g.*, frog, mouse, rat, rabbit, dog, cat cow, horse, and other organisms. Homologous nucleotide sequences also include, but are not limited to, naturally occurring allelic variations and mutations of the nucleotide sequences set forth herein. A homologous nucleotide sequence does not, however, include the exact nucleotide sequence encoding human FCTRX protein. Homologous nucleic acid sequences include those nucleic acid sequences that encode conservative amino acid substitutions (see below) in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30, as well as a polypeptide possessing FCTRX biological activity. Various biological activities of the FCTRX proteins are described below.

An FCTRX polypeptide is encoded by the open reading frame ("ORF") of an FCTRX nucleic acid. An ORF corresponds to a nucleotide sequence that could potentially be translated into a polypeptide. A stretch of nucleic acids comprising an ORF is uninterrupted by a stop codon. An ORF that represents the coding sequence for a full protein begins with an ATG "start" codon and terminates with one of the three "stop" codons, namely, TAA, TAG, or TGA. For the purposes of this invention, an ORF may be any part of a coding sequence, with or without a start codon, a stop codon, or both. For an ORF to be considered as a good candidate for coding for a *bona fide* cellular protein, a minimum size requirement is often set, *e.g.*, a stretch of DNA that would encode a protein of 50 amino acids or more.

The nucleotide sequences determined from the cloning of the human FCTRX genes allows for the generation of probes and primers designed for use in identifying and/or cloning FCTRX homologues in other cell types, *e.g.* from other tissues, as well as FCTRX homologues from other vertebrates. The probe/primer typically comprises substantially purified oligonucleotide. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 12, 25, 50, 100, 150, 200, 250, 300, 350 or 400 consecutive sense strand nucleotide sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29; or an anti-sense strand nucleotide sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29; or of a naturally occurring mutant of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29.

Probes based on the human FCTRX nucleotide sequences can be used to detect transcripts or genomic sequences encoding the same or homologous proteins. In various embodiments, the probe further comprises a label group attached thereto, *e.g.* the label group can be a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Such probes can be used as a part of a diagnostic test kit for identifying cells or tissues which mis-express an FCTRX protein, such as by measuring a level of an FCTRX-encoding nucleic acid in a sample of cells from a subject *e.g.*, detecting FCTRX mRNA levels or determining whether a genomic FCTRX gene has been mutated or deleted.

"A polypeptide having a biologically-active portion of an FCTRX polypeptide" refers to polypeptides exhibiting activity similar, but not necessarily identical to, an activity of a polypeptide of the invention, including mature forms, as measured in a particular biological assay, with or without dose dependency. A nucleic acid fragment encoding a "biologically-active portion of FCTRX" can be prepared by isolating a portion of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29, that encodes a polypeptide having an FCTRX biological activity (the biological activities of the FCTRX proteins are described below), expressing the encoded portion of FCTRX protein (*e.g.*, by recombinant expression *in vitro*) and assessing the activity of the encoded portion of FCTRX.

FCTRX Nucleic Acid and Polypeptide Variants

The invention further encompasses nucleic acid molecules that differ from the nucleotide sequences shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29, due to degeneracy of the genetic code and thus encode the same FCTRX proteins as that encoded by the nucleotide sequences shown in SEQ ID NO NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29. In another embodiment, an isolated nucleic acid molecule of the invention has a

nucleotide sequence encoding a protein having an amino acid sequence shown in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30.

In addition to the human FCTRX nucleotide sequences shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29, it will be appreciated by those skilled in the art that DNA sequence polymorphisms that lead to changes in the amino acid sequences of the FCTRX polypeptides may exist within a population (*e.g.*, the human population). Such genetic polymorphism in the FCTRX genes may exist among individuals within a population due to natural allelic variation. As used herein, the terms "gene" and "recombinant gene" refer to nucleic acid molecules comprising an open reading frame (ORF) encoding an FCTRX protein, preferably a vertebrate FCTRX protein. Such natural allelic variations can typically result in 1-5% variance in the nucleotide sequence of the FCTRX genes. Any and all such nucleotide variations and resulting amino acid polymorphisms in the FCTRX polypeptides, which are the result of natural allelic variation and that do not alter the functional activity of the FCTRX polypeptides, are intended to be within the scope of the invention.

Moreover, nucleic acid molecules encoding FCTRX proteins from other species, and thus that have a nucleotide sequence that differs from the human sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29, are intended to be within the scope of the invention. Nucleic acid molecules corresponding to natural allelic variants and homologues of the FCTRX cDNAs of the invention can be isolated based on their homology to the human FCTRX nucleic acids disclosed herein using the human cDNAs, or a portion thereof, as a hybridization probe according to standard hybridization techniques under stringent hybridization conditions.

Accordingly, in another embodiment, an isolated nucleic acid molecule of the invention is at least 6 nucleotides in length and hybridizes under stringent conditions to the nucleic acid molecule comprising the nucleotide sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29. In another embodiment, the nucleic acid is at least 10, 25, 50, 100, 250, 500, 750, 1000, 1500, or 2000 or more nucleotides in length. In yet another embodiment, an isolated nucleic acid molecule of the invention hybridizes to the coding region. As used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences at least 60% homologous to each other typically remain hybridized to each other.

Homologs (*i.e.*, nucleic acids encoding FCTRX proteins derived from species other than human) or other related sequences (*e.g.*, paralogs) can be obtained by low, moderate or high stringency hybridization with all or a portion of the particular human sequence as a probe using methods well known in the art for nucleic acid hybridization and cloning.

As used herein, the phrase "stringent hybridization conditions" refers to conditions under which a probe, primer or oligonucleotide will hybridize to its target sequence, but to no other sequences. Stringent conditions are sequence-dependent and will be different in different circumstances. Longer sequences hybridize specifically at higher temperatures than shorter sequences. Generally, stringent conditions are selected to be about 5°C lower than the thermal melting point (Tm) for the specific sequence at a defined ionic strength and pH. The Tm is the temperature (under defined ionic strength, pH and nucleic acid concentration) at which 50% of the probes complementary to the target sequence hybridize to the target sequence at equilibrium. Since the target sequences are generally present at excess, at Tm, 50% of the probes are occupied at equilibrium. Typically, stringent conditions will be those in which the salt concentration is less than about 1.0 M sodium ion, typically about 0.01 to 1.0 M sodium ion (or other salts) at

pH 7.0 to 8.3 and the temperature is at least about 30°C for short probes, primers or oligonucleotides (*e.g.*, 10 nt to 50 nt) and at least about 60°C for longer probes, primers and oligonucleotides. Stringent conditions may also be achieved with the addition of destabilizing agents, such as formamide.

Stringent conditions are known to those skilled in the art and can be found in Ausubel, *et al.*, (eds.), CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. Preferably, the conditions are such that sequences at least about 65%, 70%, 75%, 85%, 90%, 95%, 98%, or 99% homologous to each other typically remain hybridized to each other. A non-limiting example of stringent hybridization conditions are hybridization in a high salt buffer comprising 6X SSC, 50 mM Tris-HCl (pH 7.5), 1 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.02% BSA, and 500 mg/ml denatured salmon sperm DNA at 65°C, followed by one or more washes in 0.2X SSC, 0.01% BSA at 50°C. An isolated nucleic acid molecule of the invention that hybridizes under stringent conditions to the sequences of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29, corresponds to a naturally-occurring nucleic acid molecule. As used herein, a "naturally-occurring" nucleic acid molecule refers to an RNA or DNA molecule having a nucleotide sequence that occurs in nature (*e.g.*, encodes a natural protein).

In a second embodiment, a nucleic acid sequence that is hybridizable to the nucleic acid molecule comprising the nucleotide sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29, or fragments, analogs or derivatives thereof, under conditions of moderate stringency is provided. A non-limiting example of moderate stringency hybridization conditions are hybridization in 6X SSC, 5X Denhardt's solution, 0.5% SDS and 100 mg/ml denatured salmon sperm DNA at 55°C, followed by one or more washes in 1X SSC, 0.1% SDS

at 37°C. Other conditions of moderate stringency that may be used are well-known within the art. See, *e.g.*, Ausubel ,*et al.* (eds.), 1993, CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, NY, and Kriegler, 1990; GENE TRANSFER AND EXPRESSION, A LABORATORY MANUAL, Stockton Press, NY.

In a third embodiment, a nucleic acid that is hybridizable to the nucleic acid molecule comprising the nucleotide sequences of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29, or fragments, analogs or derivatives thereof, under conditions of low stringency, is provided. A non-limiting example of low stringency hybridization conditions are hybridization in 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 mg/ml denatured salmon sperm DNA, 10% (wt/vol) dextran sulfate at 40°C, followed by one or more washes in 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS at 50°C. Other conditions of low stringency that may be used are well known in the art (*e.g.*, as employed for cross-species hybridizations). See, *e.g.*, Ausubel, *et al.* (eds.), 1993, CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, NY, and Kriegler, 1990, GENE TRANSFER AND EXPRESSION, A LABORATORY MANUAL, Stockton Press, NY; Shilo and Weinberg, 1981. *Proc Natl Acad Sci USA* **78**: 6789-6792.

Conservative Mutations

In addition to naturally-occurring allelic variants of FCTRX sequences that may exist in the population, the skilled artisan will further appreciate that changes can be introduced by mutation into the nucleotide sequences of SEQ ID NO NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29, thereby leading to changes in the amino acid sequences of the encoded FCTRX proteins, without altering the functional ability of said FCTRX proteins. For example, nucleotide substitutions leading to amino acid substitutions at "non-essential" amino acid residues can be made in the sequence of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30. A "non-essential" amino acid residue is a residue that can be altered from the wild-type sequences of the FCTRX proteins without altering their biological activity, whereas an "essential" amino acid residue is required for such biological activity. For example, amino acid residues that are conserved among the FCTRX proteins of the invention are predicted to be particularly non-amenable to alteration. Amino acids for which conservative substitutions can be made are well-known within the art.

Another aspect of the invention pertains to nucleic acid molecules encoding FCTRX proteins that contain changes in amino acid residues that are not essential for activity. Such FCTRX proteins differ in amino acid sequence from SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30, yet retain biological activity. In one embodiment, the isolated nucleic acid molecule comprises a nucleotide sequence encoding a protein, wherein the protein

comprises an amino acid sequence at least about 45% homologous to the amino acid sequences of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30. Preferably, the protein encoded by the nucleic acid molecule is at least about 60% homologous to SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30; more preferably at least about 70% homologous to SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30; still more preferably at least about 80% homologous to SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30; even more preferably at least about 90% homologous to SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30; and most preferably at least about 95% homologous to SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30.

An isolated nucleic acid molecule encoding an FCTRX protein homologous to the protein of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30, can be created by introducing one or more nucleotide substitutions, additions or deletions into the nucleotide sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29, such that one or more amino acid substitutions, additions or deletions are introduced into the encoded protein.

Mutations can be introduced into SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30, by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. Preferably, conservative amino acid substitutions are made at one or more predicted, non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined within the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Thus, a predicted non-essential amino acid residue in the FCTRX protein is replaced with another amino acid residue from the same side chain family. Alternatively, in another embodiment, mutations can be introduced randomly along all or part of an FCTRX coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for FCTRX biological activity to identify mutants that retain activity. Following mutagenesis of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30, the encoded protein can be expressed by any recombinant technology known in the art and the activity of the protein can be determined.

The relatedness of amino acid families may also be determined based on side chain interactions. Substituted amino acids may be fully conserved "strong" residues or fully

conserved "weak" residues. The "strong" group of conserved amino acid residues may be any one of the following groups: STA, NEQK, NHQK, NDEQ, QHRK, MILV, MILF, HY, FYW, wherein the single letter amino acid codes are grouped by those amino acids that may be substituted for each other. Likewise, the "weak" group of conserved residues may be any one of the following: CSA, ATV, SAG, STNK, STPA, SGND, SNDEQK, NDEQHK, NEQHRK, VLIM, HFY, wherein the letters within each group represent the single letter amino acid code.

In one embodiment, a mutant FCTRX protein can be assayed for (*i*) the ability to form protein:protein interactions with other FCTRX proteins, other cell-surface proteins, or biologically-active portions thereof, (*ii*) complex formation between a mutant FCTRX protein and an FCTRX ligand; or (*iii*) the ability of a mutant FCTRX protein to bind to an intracellular target protein or biologically-active portion thereof; (*e.g.* avidin proteins).

In yet another embodiment, a mutant FCTRX protein can be assayed for the ability to regulate a specific biological function (*e.g.*, regulation of insulin release).

Antisense Nucleic Acids

Another aspect of the invention pertains to isolated antisense nucleic acid molecules that are hybridizable to or complementary to the nucleic acid molecule comprising the nucleotide sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29, or fragments, analogs or derivatives thereof. An "antisense" nucleic acid comprises a nucleotide sequence that is complementary to a "sense" nucleic acid encoding a protein (*e.g.*, complementary to the coding strand of a double-stranded cDNA molecule or complementary to an mRNA sequence). In specific aspects, antisense nucleic acid molecules are provided that comprise a sequence complementary to at least about 10, 25, 50, 100, 250 or 500 nucleotides or an entire FCTRX coding strand, or to only a portion thereof. Nucleic acid molecules encoding fragments, homologs, derivatives and analogs of an FCTRX protein of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30; or antisense nucleic acids complementary to an FCTRX nucleic acid sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29, are additionally provided.

In one embodiment, an antisense nucleic acid molecule is antisense to a "coding region" of the coding strand of a nucleotide sequence encoding an FCTRX protein. The term "coding region" refers to the region of the nucleotide sequence comprising codons which are translated into amino acid residues. In another embodiment, the antisense nucleic acid molecule is antisense to a "noncoding region" of the coding strand of a nucleotide sequence encoding the FCTRX protein. The term "noncoding region" refers to 5' and 3' sequences which flank the

coding region that are not translated into amino acids (*i.e.*, also referred to as 5' and 3' untranslated regions).

Given the coding strand sequences encoding the FCTRX protein disclosed herein, antisense nucleic acids of the invention can be designed according to the rules of Watson and Crick or Hoogsteen base pairing. The antisense nucleic acid molecule can be complementary to the entire coding region of FCTRX mRNA, but more preferably is an oligonucleotide that is antisense to only a portion of the coding or noncoding region of FCTRX mRNA. For example, the antisense oligonucleotide can be complementary to the region surrounding the translation start site of FCTRX mRNA. An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50 nucleotides in length. An antisense nucleic acid of the invention can be constructed using chemical synthesis or enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid (*e.g.*, an antisense oligonucleotide) can be chemically synthesized using naturally-occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids (*e.g.*, phosphorothioate derivatives and acridine substituted nucleotides can be used).

Examples of modified nucleotides that can be used to generate the antisense nucleic acid include: 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been subcloned in an antisense orientation (*i.e.*, RNA transcribed from the inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest, described further in the following subsection).

The antisense nucleic acid molecules of the invention are typically administered to a subject or generated *in situ* such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding an FCTRX protein to thereby inhibit expression of the protein (*e.g.*, by

inhibiting transcription and/or translation). The hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule that binds to DNA duplexes, through specific interactions in the major groove of the double helix. An example of a route of administration of antisense nucleic acid molecules of the invention includes direct injection at a tissue site. Alternatively, antisense nucleic acid molecules can be modified to target selected cells and then administered systemically. For example, for systemic administration, antisense molecules can be modified such that they specifically bind to receptors or antigens expressed on a selected cell surface (*e.g.*, by linking the antisense nucleic acid molecules to peptides or antibodies that bind to cell surface receptors or antigens). The antisense nucleic acid molecules can also be delivered to cells using the vectors described herein. To achieve sufficient nucleic acid molecules, vector constructs in which the antisense nucleic acid molecule is placed under the control of a strong pol II or pol III promoter are preferred.

In yet another embodiment, the antisense nucleic acid molecule of the invention is an α-anomeric nucleic acid molecule. An α-anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual β-units, the strands run parallel to each other. See, *e.g.,* Gaultier, *et al.*, 1987. *Nucl. Acids Res.* **15**: 6625-6641. The antisense nucleic acid molecule can also comprise a 2'-o-methylribonucleotide (see, *e.g.,* Inoue, *et al.* 1987. *Nucl. Acids Res.* **15**: 6131-6148) or a chimeric RNA-DNA analogue (see, *e.g.,* Inoue, *et al.*, 1987. *FEBS Lett.* **215**: 327-330.

Ribozymes and PNA Moieties

Nucleic acid modifications include, by way of non-limiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject.

In one embodiment, an antisense nucleic acid of the invention is a ribozyme. Ribozymes are catalytic RNA molecules with ribonuclease activity that are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. Thus, ribozymes (*e.g.*, hammerhead ribozymes as described in Haselhoff and Gerlach 1988. *Nature* 334: 585-591) can be used to catalytically cleave FCTRX mRNA transcripts to thereby inhibit translation of FCTRX mRNA. A ribozyme having specificity for an FCTRX-encoding nucleic acid can be designed based upon the nucleotide sequence of an FCTRX cDNA disclosed herein (*i.e.*, SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29). For example, a derivative of a *Tetrahymena* L-19 IVS RNA can be constructed in which the nucleotide

sequence of the active site is complementary to the nucleotide sequence to be cleaved in an FCTRX-encoding mRNA. See, *e.g.*, U.S. Patent 4,987,071 to Cech, *et al.* and U.S. Patent 5,116,742 to Cech, *et al.* FCTRX mRNA can also be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules. See, *e.g.*, Bartel *et al.*, (1993) *Science* 261:1411-1418.

Alternatively, FCTRX gene expression can be inhibited by targeting nucleotide sequences complementary to the regulatory region of the FCTRX nucleic acid (*e.g.*, the FCTRX promoter and/or enhancers) to form triple helical structures that prevent transcription of the FCTRX gene in target cells. *See, e.g.,* Helene, 1991. *Anticancer Drug Des.* 6: 569-84; Helene, *et al.* 1992. *Ann. N.Y. Acad. Sci.* 660: 27-36; Maher, 1992. *Bioassays* 14: 807-15.

In various embodiments, the FCTRX nucleic acids can be modified at the base moiety, sugar moiety or phosphate backbone to improve, *e.g.*, the stability, hybridization, or solubility of the molecule. For example, the deoxyribose phosphate backbone of the nucleic acids can be modified to generate peptide nucleic acids. *See, e.g.,* Hyrup, *et al.*, 1996. *Bioorg Med Chem* 4: 5-23. As used herein, the terms "peptide nucleic acids" or "PNAs" refer to nucleic acid mimics (*e.g.*, DNA mimics) in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases are retained. The neutral backbone of PNAs has been shown to allow for specific hybridization to DNA and RNA under conditions of low ionic strength. The synthesis of PNA oligomers can be performed using standard solid phase peptide synthesis protocols as described in Hyrup, *et al.*, 1996. *supra*; Perry-O'Keefe, *et al.*, 1996. *Proc. Natl. Acad. Sci. USA* 93: 14670-14675.

PNAs of FCTRX can be used in therapeutic and diagnostic applications. For example, PNAs can be used as antisense or antigene agents for sequence-specific modulation of gene expression by, *e.g.*, inducing transcription or translation arrest or inhibiting replication. PNAs of FCTRX can also be used, for example, in the analysis of single base pair mutations in a gene (*e.g.*, PNA directed PCR clamping; as artificial restriction enzymes when used in combination with other enzymes, *e.g.*, S_1 nucleases (*see,* Hyrup, *et al.,* 1996.*supra*); or as probes or primers for DNA sequence and hybridization (*see,* Hyrup, *et al.*, 1996, *supra*; Perry-O'Keefe, *et al.,* 1996. *supra*).

In another embodiment, PNAs of FCTRX can be modified, *e.g.*, to enhance their stability or cellular uptake, by attaching lipophilic or other helper groups to PNA, by the formation of PNA-DNA chimeras, or by the use of liposomes or other techniques of drug delivery known in the art. For example, PNA-DNA chimeras of FCTRX can be generated that may combine the advantageous properties of PNA and DNA. Such chimeras allow DNA recognition enzymes (*e.g.*, RNase H and DNA polymerases) to interact with the DNA portion while the PNA portion

would provide high binding affinity and specificity. PNA-DNA chimeras can be linked using linkers of appropriate lengths selected in terms of base stacking, number of bonds between the nucleobases, and orientation (*see,* Hyrup, etal., 1996. *supra*). The synthesis of PNA-DNA chimeras can be performed as described in Hyrup, *et al.,* 1996. *supra* and Finn, *et al.*, 1996. *Nucl Acids Res* 24: 3357-3363. For example, a DNA chain can be synthesized on a solid support using standard phosphoramidite coupling chemistry, and modified nucleoside analogs, *e.g.*, 5'-(4-methoxytrityl)amino-5'-deoxy-thymidine phosphoramidite, can be used between the PNA and the 5' end of DNA. *See, e.g.,* Mag, *et al.*, 1989. *Nucl Acid Res* 17: 5973-5988. PNA monomers are then coupled in a stepwise manner to produce a chimeric molecule with a 5' PNA segment and a 3' DNA segment. *See, e.g.,* Finn, *et al.*, 1996. *supra.* Alternatively, chimeric molecules can be synthesized with a 5' DNA segment and a 3' PNA segment. *See, e.g.,* Petersen, *et al.*, 1975. *Bioorg. Med. Chem. Lett.* 5: 1119-11124.

In other embodiments, the oligonucleotide may include other appended groups such as peptides (*e.g.*, for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (*see, e.g.*, Letsinger, *et al.*, 1989. *Proc. Natl. Acad. Sci. U.S.A.* 86: 6553-6556; Lemaitre, *et al.*, 1987. *Proc. Natl. Acad. Sci.* 84: 648-652; PCT Publication No. WO88/09810) or the blood-brain barrier (*see, e.g.*, PCT Publication No. WO 89/10134). In addition, oligonucleotides can be modified with hybridization triggered cleavage agents (*see, e.g.,* Krol, *et al.*, 1988. *BioTechniques* 6:958-976) or intercalating agents (*see, e.g.*, Zon, 1988. *Pharm. Res.* 5: 539-549). To this end, the oligonucleotide may be conjugated to another molecule, *e.g.*, a peptide, a hybridization triggered cross-linking agent, a transport agent, a hybridization-triggered cleavage agent, and the like.

FCTRX Polypeptides

A polypeptide according to the invention includes a polypeptide including the amino acid sequence of FCTRX polypeptides whose sequences are provided in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residues shown in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30, while still encoding a protein that maintains its FCTRX activities and physiological functions, or a functional fragment thereof.

In general, an FCTRX variant that preserves FCTRX-like function includes any variant in which residues at a particular position in the sequence have been substituted by other amino acids, and further include the possibility of inserting an additional residue or residues between two residues of the parent protein as well as the possibility of deleting one or more residues from

the parent sequence. Any amino acid substitution, insertion, or deletion is encompassed by the invention. In favorable circumstances, the substitution is a conservative substitution as defined above.

One aspect of the invention pertains to isolated FCTRX proteins, and biologically-active portions thereof, or derivatives, fragments, analogs or homologs thereof. Also provided are polypeptide fragments suitable for use as immunogens to raise anti-FCTRX antibodies. In one embodiment, native FCTRX proteins can be isolated from cells or tissue sources by an appropriate purification scheme using standard protein purification techniques. In another embodiment, FCTRX proteins are produced by recombinant DNA techniques. Alternative to recombinant expression, an FCTRX protein or polypeptide can be synthesized chemically using standard peptide synthesis techniques.

An "isolated" or "purified" polypeptide or protein or biologically-active portion thereof is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the FCTRX protein is derived, or substantially free from chemical precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations of FCTRX proteins in which the protein is separated from cellular components of the cells from which it is isolated or recombinantly-produced. In one embodiment, the language "substantially free of cellular material" includes preparations of FCTRX proteins having less than about 30% (by dry weight) of non-FCTRX proteins (also referred to herein as a "contaminating protein"), more preferably less than about 20% of non-FCTRX proteins, still more preferably less than about 10% of non-FCTRX proteins, and most preferably less than about 5% of non-FCTRX proteins. When the FCTRX protein or biologically-active portion thereof is recombinantly-produced, it is also preferably substantially free of culture medium, *i.e.*, culture medium represents less than about 20%, more preferably less than about 10%, and most preferably less than about 5% of the volume of the FCTRX protein preparation.

The language "substantially free of chemical precursors or other chemicals" includes preparations of FCTRX proteins in which the protein is separated from chemical precursors or other chemicals that are involved in the synthesis of the protein. In one embodiment, the language "substantially free of chemical precursors or other chemicals" includes preparations of FCTRX proteins having less than about 30% (by dry weight) of chemical precursors or non-FCTRX chemicals, more preferably less than about 20% chemical precursors or non-FCTRX chemicals, still more preferably less than about 10% chemical precursors or non-FCTRX chemicals, and most preferably less than about 5% chemical precursors or non-FCTRX chemicals.

Biologically-active portions of FCTRX proteins include peptides comprising amino acid sequences sufficiently homologous to or derived from the amino acid sequences of the FCTRX proteins (*e.g.*, the amino acid sequence shown in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30) that include fewer amino acids than the full-length FCTRX proteins, and exhibit at least one activity of an FCTRX protein. Typically, biologically-active portions comprise a domain or motif with at least one activity of the FCTRX protein. A biologically-active portion of an FCTRX protein can be a polypeptide which is, for example, 10, 25, 50, 100 or more amino acid residues in length.

Moreover, other biologically-active portions, in which other regions of the protein are deleted, can be prepared by recombinant techniques and evaluated for one or more of the functional activities of a native FCTRX protein.

In an embodiment, the FCTRX protein has an amino acid sequence shown in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30. In other embodiments, the FCTRX protein is substantially homologous to SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30, and retains the functional activity of the protein of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30, yet differs in amino acid sequence due to natural allelic variation or mutagenesis, as described in detail, below. Accordingly, in another embodiment, the FCTRX protein is a protein that comprises an amino acid sequence at least about 45% homologous to the amino acid sequence of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30, and retains the functional activity of the FCTRX proteins of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30.

Determining Homology Between Two or More Sequences

To determine the percent homology of two amino acid sequences or of two nucleic acids, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are homologous at that position (*i.e.*, as used herein amino acid or nucleic acid "homology" is equivalent to amino acid or nucleic acid "identity").

The nucleic acid sequence homology may be determined as the degree of identity between two sequences. The homology may be determined using computer programs known in the art, such as GAP software provided in the GCG program package. *See,* Needleman and Wunsch, 1970. *J Mol Biol* 48: 443-453. Using GCG GAP software with the following settings for nucleic acid sequence comparison: GAP creation penalty of 5.0 and GAP extension penalty

of 0.3, the coding region of the analogous nucleic acid sequences referred to above exhibits a degree of identity preferably of at least 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99%, with the CDS (encoding) part of the DNA sequence shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29.

The term "sequence identity" refers to the degree to which two polynucleotide or polypeptide sequences are identical on a residue-by-residue basis over a particular region of comparison. The term "percentage of sequence identity" is calculated by comparing two optimally aligned sequences over that region of comparison, determining the number of positions at which the identical nucleic acid base (*e.g.*, A, T, C, G, U, or I, in the case of nucleic acids) occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the region of comparison (*i.e.*, the window size), and multiplying the result by 100 to yield the percentage of sequence identity. The term "substantial identity" as used herein denotes a characteristic of a polynucleotide sequence, wherein the polynucleotide comprises a sequence that has at least 80 percent sequence identity, preferably at least 85 percent identity and often 90 to 95 percent sequence identity, more usually at least 99 percent sequence identity as compared to a reference sequence over a comparison region.

Chimeric and Fusion Proteins

The invention also provides FCTRX chimeric or fusion proteins. As used herein, an FCTRX "chimeric protein" or "fusion protein" comprises an FCTRX polypeptide operatively-linked to a non-FCTRX polypeptide. An "FCTRX polypeptide" refers to a polypeptide having an amino acid sequence corresponding to an FCTRX protein (SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30), whereas a "non-FCTRX polypeptide" refers to a polypeptide having an amino acid sequence corresponding to a protein that is not substantially homologous to the FCTRX protein, *e.g.*, a protein that is different from the FCTRX protein and that is derived from the same or a different organism. Within an FCTRX fusion protein the FCTRX polypeptide can correspond to all or a portion of an FCTRX protein. In one embodiment, an FCTRX fusion protein comprises at least one biologically-active portion of an FCTRX protein. In another embodiment, an FCTRX fusion protein comprises at least two biologically-active portions of an FCTRX protein. In yet another embodiment, an FCTRX fusion protein comprises at least three biologically-active portions of an FCTRX protein. Within the fusion protein, the term "operatively-linked" is intended to indicate that the FCTRX polypeptide and the non-FCTRX polypeptide are fused in-frame with one another. The non-FCTRX polypeptide can be fused to the N-terminus or C-terminus of the FCTRX polypeptide.

In one embodiment, the fusion protein is a GST-FCTRX fusion protein in which the FCTRX sequences are fused to the C-terminus of the GST (glutathione S-transferase) sequences. Such fusion proteins can facilitate the purification of recombinant FCTRX polypeptides.

In another embodiment, the fusion protein is an FCTRX protein containing a heterologous signal sequence at its N-terminus. In certain host cells (*e.g.*, mammalian host cells), expression and/or secretion of FCTRX can be increased through use of a heterologous signal sequence.

In yet another embodiment, the fusion protein is an FCTRX-immunoglobulin fusion protein in which the FCTRX sequences are fused to sequences derived from a member of the immunoglobulin protein family. The FCTRX-immunoglobulin fusion proteins of the invention can be incorporated into pharmaceutical compositions and administered to a subject to inhibit an interaction between an FCTRX ligand and an FCTRX protein on the surface of a cell, to thereby suppress FCTRX-mediated signal transduction *in vivo*. The FCTRX-immunoglobulin fusion proteins can be used to affect the bioavailability of an FCTRX cognate ligand. Inhibition of the FCTRX ligand/FCTRX interaction may be useful therapeutically for both the treatment of proliferative and differentiative disorders, as well as modulating (*e.g.* promoting or inhibiting) cell survival. Moreover, the FCTRX-immunoglobulin fusion proteins of the invention can be used as immunogens to produce anti-FCTRX antibodies in a subject, to purify FCTRX ligands, and in screening assays to identify molecules that inhibit the interaction of FCTRX with an FCTRX ligand.

An FCTRX chimeric or fusion protein of the invention can be produced by standard recombinant DNA techniques. For example, DNA fragments coding for the different polypeptide sequences are ligated together in-frame in accordance with conventional techniques, *e.g.*, by employing blunt-ended or stagger-ended termini for ligation, restriction enzyme digestion to provide for appropriate termini, filling-in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and enzymatic ligation. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers that give rise to complementary overhangs between two consecutive gene fragments that can subsequently be annealed and reamplified to generate a chimeric gene sequence (*see, e.g.,* Ausubel, *et al.* (eds.) CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, 1992). Moreover, many expression vectors are commercially available that already encode a fusion moiety (*e.g.*, a GST polypeptide). An FCTRX-encoding nucleic acid can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the FCTRX protein.

FCTRX Agonists and Antagonists

The invention also pertains to variants of the FCTRX proteins that function as either FCTRX agonists (*i.e.*, mimetics) or as FCTRX antagonists. Variants of the FCTRX protein can be generated by mutagenesis (*e.g.*, discrete point mutation or truncation of the FCTRX protein). An agonist of the FCTRX protein can retain substantially the same, or a subset of, the biological activities of the naturally occurring form of the FCTRX protein. An antagonist of the FCTRX protein can inhibit one or more of the activities of the naturally occurring form of the FCTRX protein by, for example, competitively binding to a downstream or upstream member of a cellular signaling cascade which includes the FCTRX protein. Thus, specific biological effects can be elicited by treatment with a variant of limited function. In one embodiment, treatment of a subject with a variant having a subset of the biological activities of the naturally occurring form of the protein has fewer side effects in a subject relative to treatment with the naturally occurring form of the FCTRX proteins.

Variants of the FCTRX proteins that function as either FCTRX agonists (*i.e.*, mimetics) or as FCTRX antagonists can be identified by screening combinatorial libraries of mutants (*e.g.*, truncation mutants) of the FCTRX proteins for FCTRX protein agonist or antagonist activity. In one embodiment, a variegated library of FCTRX variants is generated by combinatorial mutagenesis at the nucleic acid level and is encoded by a variegated gene library. A variegated library of FCTRX variants can be produced by, for example, enzymatically ligating a mixture of synthetic oligonucleotides into gene sequences such that a degenerate set of potential FCTRX sequences is expressible as individual polypeptides, or alternatively, as a set of larger fusion proteins (*e.g.*, for phage display) containing the set of FCTRX sequences therein. There are a variety of methods which can be used to produce libraries of potential FCTRX variants from a degenerate oligonucleotide sequence. Chemical synthesis of a degenerate gene sequence can be performed in an automatic DNA synthesizer, and the synthetic gene then ligated into an appropriate expression vector. Use of a degenerate set of genes allows for the provision, in one mixture, of all of the sequences encoding the desired set of potential FCTRX sequences. Methods for synthesizing degenerate oligonucleotides are well-known within the art. *See, e.g.*, Narang, 1983. *Tetrahedron* 39: 3; Itakura, *et al.*, 1984. *Annu. Rev. Biochem.* 53: 323; Itakura, *et al.*, 1984. *Science* 198: 1056; Ike, *et al.*, 1983. *Nucl. Acids Res.* 11: 477.

Polypeptide Libraries

In addition, libraries of fragments of the FCTRX protein coding sequences can be used to generate a variegated population of FCTRX fragments for screening and subsequent selection of variants of an FCTRX protein. In one embodiment, a library of coding sequence fragments can be generated by treating a double stranded PCR fragment of an FCTRX coding sequence with a

nuclease under conditions wherein nicking occurs only about once per molecule, denaturing the double stranded DNA, renaturing the DNA to form double-stranded DNA that can include sense/antisense pairs from different nicked products, removing single stranded portions from reformed duplexes by treatment with S_1 nuclease, and ligating the resulting fragment library into an expression vector. By this method, expression libraries can be derived which encodes N-terminal and internal fragments of various sizes of the FCTRX proteins.

Various techniques are known in the art for screening gene products of combinatorial libraries made by point mutations or truncation, and for screening cDNA libraries for gene products having a selected property. Such techniques are adaptable for rapid screening of the gene libraries generated by the combinatorial mutagenesis of FCTRX proteins. The most widely used techniques, which are amenable to high throughput analysis, for screening large gene libraries typically include cloning the gene library into replicable expression vectors, transforming appropriate cells with the resulting library of vectors, and expressing the combinatorial genes under conditions in which detection of a desired activity facilitates isolation of the vector encoding the gene whose product was detected. Recursive ensemble mutagenesis (REM), a new technique that enhances the frequency of functional mutants in the libraries, can be used in combination with the screening assays to identify FCTRX variants. *See, e.g.,* Arkin and Yourvan, 1992. *Proc. Natl. Acad. Sci. USA* 89: 7811-7815; Delgrave, *et al.*, 1993. *Protein Engineering* 6:327-331.

Anti-FCTRX Antibodies

The invention encompasses antibodies and antibody fragments, such as F_{ab} or $(F_{ab})_2$, that bind immunospecifically to any of the FCTRX polypeptides of said invention.

An isolated FCTRX protein, or a portion or fragment thereof, can be used as an immunogen to generate antibodies that bind to FCTRX polypeptides using standard techniques for polyclonal and monoclonal antibody preparation. The full-length FCTRX proteins can be used or, alternatively, the invention provides antigenic peptide fragments of FCTRX proteins for use as immunogens. The antigenic FCTRX peptides comprises at least 4 amino acid residues of the amino acid sequence shown in SEQ ID NO NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30, and encompasses an epitope of FCTRX such that an antibody raised against the peptide forms a specific immune complex with FCTRX. Preferably, the antigenic peptide comprises at least 6, 8, 10, 15, 20, or 30 amino acid residues. Longer antigenic peptides are sometimes preferable over shorter antigenic peptides, depending on use and according to methods well known to someone skilled in the art.

In certain embodiments of the invention, at least one epitope encompassed by the antigenic peptide is a region of FCTRX that is located on the surface of the protein (*e.g.*, a hydrophilic region). As a means for targeting antibody production, hydropathy plots showing regions of hydrophilicity and hydrophobicity may be generated by any method well known in the art, including, for example, the Kyte Doolittle or the Hopp Woods methods, either with or without Fourier transformation (*see, e.g.*, Hopp and Woods, 1981. *Proc. Nat. Acad. Sci. USA* 78: 3824-3828; Kyte and Doolittle, 1982. *J. Mol. Biol.* 157: 105-142, each incorporated herein by reference in their entirety).

As disclosed herein, FCTRX protein sequences of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30, or derivatives, fragments, analogs or homologs thereof, may be utilized as immunogens in the generation of antibodies that immunospecifically-bind these protein components. The term "antibody" as used herein refers to immunoglobulin molecules and immunologically-active portions of immunoglobulin molecules, *i.e.*, molecules that contain an antigen binding site that specifically-binds (immunoreacts with) an antigen, such as FCTRX. Such antibodies include, but are not limited to, polyclonal, monoclonal, chimeric, single chain, F_{ab} and $F_{(ab')2}$ fragments, and an F_{ab} expression library. In a specific embodiment, antibodies to human FCTRX proteins are disclosed. Various procedures known within the art may be used for the production of polyclonal or monoclonal antibodies to an FCTRX protein sequence of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30, or a derivative, fragment, analog or homolog thereof. Some of these proteins are discussed below.

For the production of polyclonal antibodies, various suitable host animals (*e.g.*, rabbit, goat, mouse or other mammal) may be immunized by injection with the native protein, or a synthetic variant thereof, or a derivative of the foregoing. An appropriate immunogenic preparation can contain, for example, recombinantly-expressed FCTRX protein or a chemically-synthesized FCTRX polypeptide. The preparation can further include an adjuvant. Various adjuvants used to increase the immunological response include, but are not limited to, Freund's (complete and incomplete), mineral gels (*e.g.,* aluminum hydroxide), surface active substances (*e.g.,* lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, dinitrophenol, etc.), human adjuvants such as *Bacille Calmette-Guerin* and *Corynebacterium parvum*, or similar immunostimulatory agents. If desired, the antibody molecules directed against FCTRX can be isolated from the mammal (*e.g.*, from the blood) and further purified by well known techniques, such as protein A chromatography to obtain the IgG fraction.

The term "monoclonal antibody" or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one species of an antigen binding site capable of immunoreacting with a particular epitope of FCTRX. A monoclonal antibody

composition thus typically displays a single binding affinity for a particular FCTRX protein with which it immunoreacts. For preparation of monoclonal antibodies directed towards a particular FCTRX protein, or derivatives, fragments, analogs or homologs thereof, any technique that provides for the production of antibody molecules by continuous cell line culture may be utilized. Such techniques include, but are not limited to, the hybridoma technique (*see, e.g.,* Kohler & Milstein, 1975. *Nature* 256: 495-497); the trioma technique; the human B-cell hybridoma technique (*see, e.g.,* Kozbor, *et al.,* 1983. *Immunol. Today* 4: 72) and the EBV hybridoma technique to produce human monoclonal antibodies (*see, e.g.,* Cole, *et al.,* 1985. In: MONOCLONAL ANTIBODIES AND CANCER THERAPY, Alan R. Liss, Inc., pp. 77-96). Human monoclonal antibodies may be utilized in the practice of the invention and may be produced by using human hybridomas (*see, e.g.,* Cote, *et al.,* 1983. *Proc Natl Acad Sci USA* 80: 2026-2030) or by transforming human B-cells with Epstein Barr Virus *in vitro* (*see, e.g.,* Cole, *et al.,* 1985. In: MONOCLONAL ANTIBODIES AND CANCER THERAPY, Alan R. Liss, Inc., pp. 77-96). Each of the above citations is incorporated herein by reference in their entirety.

According to the invention, techniques can be adapted for the production of single-chain antibodies specific to an FCTRX protein (*see, e.g.,* U.S. Patent No. 4,946,778). In addition, methods can be adapted for the construction of F_{ab} expression libraries (*see, e.g.,* Huse, *et al.,* 1989. *Science* 246: 1275-1281) to allow rapid and effective identification of monoclonal F_{ab} fragments with the desired specificity for an FCTRX protein or derivatives, fragments, analogs or homologs thereof. Non-human antibodies can be "humanized" by techniques well known in the art. *See, e.g.,* U.S. Patent No. 5,225,539. Antibody fragments that contain the idiotypes to an FCTRX protein may be produced by techniques known in the art including, but not limited to: (*i*) an $F_{(ab')2}$ fragment produced by pepsin digestion of an antibody molecule; (*ii*) an F_{ab} fragment generated by reducing the disulfide bridges of an $F_{(ab')2}$ fragment; (*iii*) an F_{ab} fragment generated by the treatment of the antibody molecule with papain and a reducing agent; and (*iv*) F_v fragments.

Additionally, recombinant anti-FCTRX antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which can be made using standard recombinant DNA techniques, are within the scope of the invention. Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art, for example using methods described in International Application No. PCT/US86/02269; European Patent Application No. 184,187; European Patent Application No. 171,496; European Patent Application No. 173,494; PCT International Publication No. WO 86/01533; U.S. Patent No. 4,816,567; U.S. Pat. No. 5,225,539; European Patent Application No. 125,023; Better, *et al.*, 1988. *Science* 240: 1041-1043; Liu, *et al.*, 1987. *Proc. Natl. Acad. Sci.*

USA 84: 3439-3443; Liu, *et al.*, 1987. *J. Immunol.* 139: 3521-3526; Sun, *et al.*, 1987. *Proc. Natl. Acad. Sci. USA* 84: 214-218; Nishimura, *et al.*, 1987. *Cancer Res.* 47: 999-1005; Wood, *et al.*, 1985. *Nature* 314 :446-449; Shaw, *et al.*, 1988. *J. Natl. Cancer Inst.* 80: 1553-1559); Morrison(1985) *Science* 229:1202-1207; Oi, *et al.* (1986) *BioTechniques* 4:214; Jones, *et al.*, 1986. *Nature* 321: 552-525; Verhoeyan, *et al.*, 1988. *Science* 239: 1534; and Beidler, *et al.*, 1988. *J. Immunol.* 141: 4053-4060. Each of the above citations are incorporated herein by reference in their entirety.

In one embodiment, methods for the screening of antibodies that possess the desired specificity include, but are not limited to, enzyme-linked immunosorbent assay (ELISA) and other immunologically-mediated techniques known within the art. In a specific embodiment, selection of antibodies that are specific to a particular domain of an FCTRX protein is facilitated by generation of hybridomas that bind to the fragment of an FCTRX protein possessing such a domain. Thus, antibodies that are specific for a desired domain within an FCTRX protein, or derivatives, fragments, analogs or homologs thereof, are also provided herein.

Anti-FCTRX antibodies may be used in methods known within the art relating to the localization and/or quantitation of an FCTRX protein (*e.g.,* for use in measuring levels of the FCTRX protein within appropriate physiological samples, for use in diagnostic methods, for use in imaging the protein, and the like). In a given embodiment, antibodies for FCTRX proteins, or derivatives, fragments, analogs or homologs thereof, that contain the antibody derived binding domain, are utilized as pharmacologically-active compounds (hereinafter "Therapeutics").

An anti-FCTRX antibody (*e.g.*, monoclonal antibody) can be used to isolate an FCTRX polypeptide by standard techniques, such as affinity chromatography or immunoprecipitation. An anti-FCTRX antibody can facilitate the purification of natural FCTRX polypeptide from cells and of recombinantly-produced FCTRX polypeptide expressed in host cells. Moreover, an anti-FCTRX antibody can be used to detect FCTRX protein (*e.g.*, in a cellular lysate or cell supernatant) in order to evaluate the abundance and pattern of expression of the FCTRX protein. Anti-FCTRX antibodies can be used diagnostically to monitor protein levels in tissue as part of a clinical testing procedure, *e.g.*, to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling (*i.e.*, physically linking) the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine

fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I, ^{131}I, ^{35}S or ^{3}H.

FCTRX Recombinant Expression Vectors and Host Cells

Another aspect of the invention pertains to vectors, preferably expression vectors, containing a nucleic acid encoding an FCTRX protein, or derivatives, fragments, analogs or homologs thereof. As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively-linked. Such vectors are referred to herein as "expression vectors". In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" can be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

The recombinant expression vectors of the invention comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell, which means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, that is operatively-linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably-linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner that allows for expression of the nucleotide sequence (*e.g.*, in an *in vitro* transcription/translation system or in a host cell when the vector is introduced into the host cell).

The term "regulatory sequence" is intended to includes promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals). Such regulatory sequences are described, for example, in Goeddel, GENE EXPRESSION TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990). Regulatory sequences include

those that direct constitutive expression of a nucleotide sequence in many types of host cell and those that direct expression of the nucleotide sequence only in certain host cells (*e.g.*, tissue-specific regulatory sequences). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, etc. The expression vectors of the invention can be introduced into host cells to thereby produce proteins or peptides, including fusion proteins or peptides, encoded by nucleic acids as described herein (*e.g.*, FCTRX proteins, mutant forms of FCTRX proteins, fusion proteins, etc.).

The recombinant expression vectors of the invention can be designed for expression of FCTRX proteins in prokaryotic or eukaryotic cells. For example, FCTRX proteins can be expressed in bacterial cells such as *Escherichia coli*, insect cells (using baculovirus expression vectors) yeast cells or mammalian cells. Suitable host cells are discussed further in Goeddel, GENE EXPRESSION TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990). Alternatively, the recombinant expression vector can be transcribed and translated *in vitro*, for example using T7 promoter regulatory sequences and T7 polymerase.

Expression of proteins in prokaryotes is most often carried out in *Escherichia coli* with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion proteins. Fusion vectors add a number of amino acids to a protein encoded therein, usually to the amino terminus of the recombinant protein. Such fusion vectors typically serve three purposes: (*i*) to increase expression of recombinant protein; (*ii*) to increase the solubility of the recombinant protein; and (*iii*) to aid in the purification of the recombinant protein by acting as a ligand in affinity purification. Often, in fusion expression vectors, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant protein to enable separation of the recombinant protein from the fusion moiety subsequent to purification of the fusion protein. Such enzymes, and their cognate recognition sequences, include Factor Xa, thrombin and enterokinase. Typical fusion expression vectors include pGEX (Pharmacia Biotech Inc; Smith and Johnson, 1988. *Gene* 67: 31-40), pMAL (New England Biolabs, Beverly, Mass.) and pRIT5 (Pharmacia, Piscataway, N.J.) that fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein.

Examples of suitable inducible non-fusion *E. coli* expression vectors include pTrc (Amrann *et al.*, (1988) *Gene* 69:301-315) and pET 11d (Studier *et al.*, GENE EXPRESSION TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990) 60-89).

One strategy to maximize recombinant protein expression in *E. coli* is to express the protein in a host bacteria with an impaired capacity to proteolytically cleave the recombinant protein. *See, e.g.,* Gottesman, GENE EXPRESSION TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990) 119-128. Another strategy is to alter the nucleic acid sequence of the nucleic acid to be inserted into an expression vector so that the individual codons for each amino acid are those preferentially utilized in *E. coli* (*see, e.g.,* Wada, *et al.*, 1992. *Nucl. Acids Res.* 20: 2111-2118). Such alteration of nucleic acid sequences of the invention can be carried out by standard DNA synthesis techniques.

In another embodiment, the FCTRX expression vector is a yeast expression vector. Examples of vectors for expression in yeast *Saccharomyces cerivisae* include pYepSec1 (Baldari, *et al.*, 1987. *EMBO J.* 6: 229-234), pMFa (Kurjan and Herskowitz, 1982. *Cell* 30: 933-943), pJRY88 (Schultz *et al.*, 1987. *Gene* 54: 113-123), pYES2 (Invitrogen Corporation, San Diego, Calif.), and picZ (InVitrogen Corp, San Diego, Calif.).

Alternatively, FCTRX can be expressed in insect cells using baculovirus expression vectors. Baculovirus vectors available for expression of proteins in cultured insect cells (*e.g.*, SF9 cells) include the pAc series (Smith, *et al.*, 1983. *Mol. Cell. Biol.* 3: 2156-2165) and the pVL series (Lucklow and Summers, 1989. *Virology* 170: 31-39).

In yet another embodiment, a nucleic acid of the invention is expressed in mammalian cells using a mammalian expression vector. Examples of mammalian expression vectors include pCDM8 (Seed, 1987. *Nature* 329: 840) and pMT2PC (Kaufman, *et al.*, 1987. *EMBO J.* 6: 187-195). When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements. For example, commonly used promoters are derived from polyoma, adenovirus 2, cytomegalovirus, and simian virus 40. For other suitable expression systems for both prokaryotic and eukaryotic cells see, *e.g.*, Chapters 16 and 17 of Sambrook, *et al.*, MOLECULAR CLONING: A LABORATORY MANUAL. 2nd ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989.

In another embodiment, the recombinant mammalian expression vector is capable of directing expression of the nucleic acid preferentially in a particular cell type (*e.g.*, tissue-specific regulatory elements are used to express the nucleic acid). Tissue-specific regulatory elements are known in the art. Non-limiting examples of suitable tissue-specific promoters include the albumin promoter (liver-specific; Pinkert, *et al.*, 1987. *Genes Dev.* 1: 268-277), lymphoid-specific promoters (Calame and Eaton, 1988. *Adv. Immunol.* 43: 235-275), in particular promoters of T cell receptors (Winoto and Baltimore, 1989. *EMBO J.* 8: 729-733) and immunoglobulins (Banerji, *et al.*, 1983. *Cell* 33: 729-740; Queen and Baltimore, 1983. *Cell* 33: 741-748), neuron-specific promoters (*e.g.*, the neurofilament promoter; Byrne and Ruddle,

1989. *Proc. Natl. Acad. Sci. USA* 86: 5473-5477), pancreas-specific promoters (Edlund, *et al.*, 1985. *Science* 230: 912-916), and mammary gland-specific promoters (*e.g.*, milk whey promoter; U.S. Pat. No. 4,873,316 and European Application Publication No. 264,166). Developmentally-regulated promoters are also encompassed, *e.g.*, the murine hox promoters (Kessel and Gruss, 1990. *Science* 249: 374-379) and the α-fetoprotein promoter (Campes and Tilghman, 1989. *Genes Dev.* 3: 537-546).

The invention further provides a recombinant expression vector comprising a DNA molecule of the invention cloned into the expression vector in an antisense orientation. That is, the DNA molecule is operatively-linked to a regulatory sequence in a manner that allows for expression (by transcription of the DNA molecule) of an RNA molecule that is antisense to FCTRX mRNA. Regulatory sequences operatively linked to a nucleic acid cloned in the antisense orientation can be chosen that direct the continuous expression of the antisense RNA molecule in a variety of cell types, for instance viral promoters and/or enhancers, or regulatory sequences can be chosen that direct constitutive, tissue specific or cell type specific expression of antisense RNA. The antisense expression vector can be in the form of a recombinant plasmid, phagemid or attenuated virus in which antisense nucleic acids are produced under the control of a high efficiency regulatory region, the activity of which can be determined by the cell type into which the vector is introduced. For a discussion of the regulation of gene expression using antisense genes *see, e.g.,* Weintraub, *et al.*, "Antisense RNA as a molecular tool for genetic analysis," *Reviews-Trends in Genetics*, Vol. 1(1) 1986.

Another aspect of the invention pertains to host cells into which a recombinant expression vector of the invention has been introduced. The terms "host cell" and "recombinant host cell" are used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but also to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

A host cell can be any prokaryotic or eukaryotic cell. For example, FCTRX protein can be expressed in bacterial cells such as *E. coli*, insect cells, yeast or mammalian cells (such as Chinese hamster ovary cells (CHO) or COS cells). Other suitable host cells are known to those skilled in the art.

Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid (*e.g.*, DNA) into a host cell, including calcium phosphate or calcium

chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook, *et al.* (MOLECULAR CLONING: A LABORATORY MANUAL. 2nd ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989), and other laboratory manuals.

For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells may integrate the foreign DNA into their genome. In order to identify and select these integrants, a gene that encodes a selectable marker (*e.g.*, resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. Various selectable markers include those that confer resistance to drugs, such as G418, hygromycin and methotrexate. Nucleic acid encoding a selectable marker can be introduced into a host cell on the same vector as that encoding FCTRX or can be introduced on a separate vector. Cells stably transfected with the introduced nucleic acid can be identified by drug selection (*e.g.*, cells that have incorporated the selectable marker gene will survive, while the other cells die).

A host cell of the invention, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce (*i.e.*, express) FCTRX protein. Accordingly, the invention further provides methods for producing FCTRX protein using the host cells of the invention. In one embodiment, the method comprises culturing the host cell of invention (into which a recombinant expression vector encoding FCTRX protein has been introduced) in a suitable medium such that FCTRX protein is produced. In another embodiment, the method further comprises isolating FCTRX protein from the medium or the host cell.

Transgenic FCTRX Animals

The host cells of the invention can also be used to produce non-human transgenic animals. For example, in one embodiment, a host cell of the invention is a fertilized oocyte or an embryonic stem cell into which FCTRX protein-coding sequences have been introduced. Such host cells can then be used to create non-human transgenic animals in which exogenous FCTRX sequences have been introduced into their genome or homologous recombinant animals in which endogenous FCTRX sequences have been altered. Such animals are useful for studying the function and/or activity of FCTRX protein and for identifying and/or evaluating modulators of FCTRX protein activity. As used herein, a "transgenic animal" is a non-human animal, preferably a mammal, more preferably a rodent such as a rat or mouse, in which one or more of the cells of the animal includes a transgene. Other examples of transgenic animals include non-human primates, sheep, dogs, cows, goats, chickens, amphibians, etc. A transgene

is exogenous DNA that is integrated into the genome of a cell from which a transgenic animal develops and that remains in the genome of the mature animal, thereby directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal. As used herein, a "homologous recombinant animal" is a non-human animal, preferably a mammal, more preferably a mouse, in which an endogenous FCTRX gene has been altered by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the animal, *e.g.*, an embryonic cell of the animal, prior to development of the animal.

A transgenic animal of the invention can be created by introducing FCTRX-encoding nucleic acid into the male pronuclei of a fertilized oocyte (*e.g.*, by microinjection, retroviral infection) and allowing the oocyte to develop in a pseudopregnant female foster animal. The human FCTRX cDNA sequences of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29, can be introduced as a transgene into the genome of a non-human animal. Alternatively, a non-human homologue of the human FCTRX gene, such as a mouse FCTRX gene, can be isolated based on hybridization to the human FCTRX cDNA (described further *supra*) and used as a transgene. Intronic sequences and polyadenylation signals can also be included in the transgene to increase the efficiency of expression of the transgene. A tissue-specific regulatory sequence(s) can be operably-linked to the FCTRX transgene to direct expression of FCTRX protein to particular cells. Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866; 4,870,009; and 4,873,191; and Hogan, 1986. In: MANIPULATING THE MOUSE EMBRYO, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. Similar methods are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence of the FCTRX transgene in its genome and/or expression of FCTRX mRNA in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying a transgene-encoding FCTRX protein can further be bred to other transgenic animals carrying other transgenes.

To create a homologous recombinant animal, a vector is prepared which contains at least a portion of an FCTRX gene into which a deletion, addition or substitution has been introduced to thereby alter, *e.g.*, functionally disrupt, the FCTRX gene. The FCTRX gene can be a human gene (*e.g.*, the cDNA of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29), but more preferably, is a non-human homologue of a human FCTRX gene. For example, a mouse homologue of human FCTRX gene of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29, can be used to construct a homologous recombination vector suitable for

altering an endogenous FCTRX gene in the mouse genome. In one embodiment, the vector is designed such that, upon homologous recombination, the endogenous FCTRX gene is functionally disrupted (*i.e.*, no longer encodes a functional protein; also referred to as a "knock out" vector).

Alternatively, the vector can be designed such that, upon homologous recombination, the endogenous FCTRX gene is mutated or otherwise altered but still encodes functional protein (*e.g.*, the upstream regulatory region can be altered to thereby alter the expression of the endogenous FCTRX protein). In the homologous recombination vector, the altered portion of the FCTRX gene is flanked at its 5'- and 3'-termini by additional nucleic acid of the FCTRX gene to allow for homologous recombination to occur between the exogenous FCTRX gene carried by the vector and an endogenous FCTRX gene in an embryonic stem cell. The additional flanking FCTRX nucleic acid is of sufficient length for successful homologous recombination with the endogenous gene. Typically, several kilobases of flanking DNA (both at the 5'- and 3'-termini) are included in the vector. *See, e.g.,* Thomas, *et al.*, 1987. *Cell* 51: 503 for a description of homologous recombination vectors. The vector is ten introduced into an embryonic stem cell line (*e.g.*, by electroporation) and cells in which the introduced FCTRX gene has homologously-recombined with the endogenous FCTRX gene are selected. *See, e.g.*, Li, *et al.*, 1992. *Cell* 69: 915.

The selected cells are then injected into a blastocyst of an animal (*e.g.*, a mouse) to form aggregation chimeras. *See, e.g.*, Bradley, 1987. In: TERATOCARCINOMAS AND EMBRYONIC STEM CELLS: A PRACTICAL APPROACH, Robertson, ed. IRL, Oxford, pp. 113-152. A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term. Progeny harboring the homologously-recombined DNA in their germ cells can be used to breed animals in which all cells of the animal contain the homologously-recombined DNA by germline transmission of the transgene. Methods for constructing homologous recombination vectors and homologous recombinant animals are described further in Bradley, 1991. *Curr. Opin. Biotechnol.* 2: 823-829; PCT International Publication Nos.: WO 90/11354; WO 91/01140; WO 92/0968; and WO 93/04169.

In another embodiment, transgenic non-humans animals can be produced that contain selected systems that allow for regulated expression of the transgene. One example of such a system is the cre/loxP recombinase system of bacteriophage P1. For a description of the cre/loxP recombinase system, *See, e.g.*, Lakso, *et al.*, 1992. *Proc. Natl. Acad. Sci. USA* 89: 6232-6236. Another example of a recombinase system is the FLP recombinase system of *Saccharomyces cerevisiae. See,* O'Gorman, *et al.*, 1991. *Science* 251:1351-1355. If a cre/loxP recombinase system is used to regulate expression of the transgene, animals containing

transgenes encoding both the Cre recombinase and a selected protein are required. Such animals can be provided through the construction of "double" transgenic animals, *e.g.*, by mating two transgenic animals, one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase.

Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmut, *et al.*, 1997. *Nature* 385: 810-813. In brief, a cell (*e.g.*, a somatic cell) from the transgenic animal can be isolated and induced to exit the growth cycle and enter G_0 phase. The quiescent cell can then be fused, *e.g.*, through the use of electrical pulses, to an enucleated oocyte from an animal of the same species from which the quiescent cell is isolated. The reconstructed oocyte is then cultured such that it develops to morula or blastocyte and then transferred to pseudopregnant female foster animal. The offspring borne of this female foster animal will be a clone of the animal from which the cell (*e.g.*, the somatic cell) is isolated.

Pharmaceutical Compositions

The FCTRX nucleic acid molecules, FCTRX proteins, and anti-FCTRX antibodies (also referred to herein as "active compounds") of the invention, and derivatives, fragments, analogs and homologs thereof, can be incorporated into pharmaceutical compositions suitable for administration. Such compositions typically comprise the nucleic acid molecule, protein, or antibody and a pharmaceutically acceptable carrier. As used herein, "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. Suitable carriers are described in the most recent edition of Remington's Pharmaceutical Sciences, a standard reference text in the field, which is incorporated herein by reference. Preferred examples of such carriers or diluents include, but are not limited to, water, saline, finger's solutions, dextrose solution, and 5% human serum albumin. Liposomes and non-aqueous vehicles such as fixed oils may also be used. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), transdermal (*i.e.*, topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral,

intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid (EDTA); buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound (*e.g.*, an FCTRX protein or anti-FCTRX antibody) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of

the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

The compounds can also be prepared in the form of suppositories (*e.g.*, with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including

liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

The nucleic acid molecules of the invention can be inserted into vectors and used as gene therapy vectors. Gene therapy vectors can be delivered to a subject by, for example, intravenous injection, local administration (*see, e.g.,* U.S. Patent No. 5,328,470) or by stereotactic injection (*see, e.g.*, Chen, *et al.*, 1994. *Proc. Natl. Acad. Sci. USA* 91: 3054-3057). The pharmaceutical preparation of the gene therapy vector can include the gene therapy vector in an acceptable diluent, or can comprise a slow release matrix in which the gene delivery vehicle is imbedded. Alternatively, where the complete gene delivery vector can be produced intact from recombinant cells, *e.g.*, retroviral vectors, the pharmaceutical preparation can include one or more cells that produce the gene delivery system.

The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

Screening and Detection Methods

The isolated nucleic acid molecules of the invention can be used to express FCTRX protein (*e.g.*, via a recombinant expression vector in a host cell in gene therapy applications), to detect FCTRX mRNA (*e.g.*, in a biological sample) or a genetic lesion in an FCTRX gene, and to modulate FCTRX activity, as described further, below. In addition, the FCTRX proteins can be used to screen drugs or compounds that modulate the FCTRX protein activity or expression as well as to treat disorders characterized by insufficient or excessive production of FCTRX protein or production of FCTRX protein forms that have decreased or aberrant activity compared to FCTRX wild-type protein (*e.g.*; diabetes (regulates insulin release); obesity (binds and transport lipids); metabolic disturbances associated with obesity, the metabolic syndrome X as well as anorexia and wasting disorders associated with chronic diseases and various cancers,

and infectious disease(possesses anti-microbial activity) and the various dyslipidemias. In addition, the anti-FCTRX antibodies of the invention can be used to detect and isolate FCTRX proteins and modulate FCTRX activity. In yet a further aspect, the invention can be used in methods to influence appetite, absorption of nutrients and the disposition of metabolic substrates in both a positive and negative fashion.

The invention further pertains to novel agents identified by the screening assays described herein and uses thereof for treatments as described, *supra*.

Screening Assays

The invention provides a method (also referred to herein as a "screening assay") for identifying modulators, *i.e.*, candidate or test compounds or agents (*e.g.*, peptides, peptidomimetics, small molecules or other drugs) that bind to FCTRX proteins or have a stimulatory or inhibitory effect on, *e.g.*, FCTRX protein expression or FCTRX protein activity. The invention also includes compounds identified in the screening assays described herein.

In one embodiment, the invention provides assays for screening candidate or test compounds which bind to or modulate the activity of the membrane-bound form of an FCTRX protein or polypeptide or biologically-active portion thereof. The test compounds of the invention can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the "one-bead one-compound" library method; and synthetic library methods using affinity chromatography selection. The biological library approach is limited to peptide libraries, while the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds. *See, e.g.,* Lam, 1997. *Anticancer Drug Design* 12: 145.

A "small molecule" as used herein, is meant to refer to a composition that has a molecular weight of less than about 5 kD and most preferably less than about 4 kD. Small molecules can be, *e.g.*, nucleic acids, peptides, polypeptides, peptidomimetics, carbohydrates, lipids or other organic or inorganic molecules. Libraries of chemical and/or biological mixtures, such as fungal, bacterial, or algal extracts, are known in the art and can be screened with any of the assays of the invention.

Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt, *et al.*, 1993. *Proc. Natl. Acad. Sci. U.S.A.* 90: 6909; Erb, *et al.*, 1994. *Proc. Natl. Acad. Sci. U.S.A.* 91: 11422; Zuckermann, *et al.*, 1994. *J. Med. Chem.* 37: 2678; Cho, *et al.*, 1993. *Science* 261: 1303; Carrell, *et al.*, 1994. *Angew. Chem. Int. Ed. Engl.* 33: 2059; Carell, *et al.*, 1994. *Angew. Chem. Int. Ed. Engl.* 33: 2061; and Gallop, *et al.*, 1994. *J. Med. Chem.* 37: 1233.

Libraries of compounds may be presented in solution (*e.g.*, Houghten, 1992. *Biotechniques* 13: 412-421), or on beads (Lam, 1991. *Nature* 354: 82-84), on chips (Fodor, 1993. *Nature* 364: 555-556), bacteria (Ladner, U.S. Patent No. 5,223,409), spores (Ladner, U.S. Patent 5,233,409), plasmids (Cull, *et al.*, 1992. *Proc. Natl. Acad. Sci. USA* 89: 1865-1869) or on phage (Scott and Smith, 1990. *Science* 249: 386-390; Devlin, 1990. *Science* 249: 404-406; Cwirla, *et al.*, 1990. *Proc. Natl. Acad. Sci. U.S.A.* 87: 6378-6382; Felici, 1991. *J. Mol. Biol.* 222: 301-310; Ladner, U.S. Patent No. 5,233,409.).

In one embodiment, an assay is a cell-based assay in which a cell which expresses a membrane-bound form of FCTRX protein, or a biologically-active portion thereof, on the cell surface is contacted with a test compound and the ability of the test compound to bind to an FCTRX protein determined. The cell, for example, can of mammalian origin or a yeast cell. Determining the ability of the test compound to bind to the FCTRX protein can be accomplished, for example, by coupling the test compound with a radioisotope or enzymatic label such that binding of the test compound to the FCTRX protein or biologically-active portion thereof can be determined by detecting the labeled compound in a complex. For example, test compounds can be labeled with ^{125}I, ^{35}S, ^{14}C, or ^{3}H, either directly or indirectly, and the radioisotope detected by direct counting of radioemission or by scintillation counting. Alternatively, test compounds can be enzymatically-labeled with, for example, horseradish peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product. In one embodiment, the assay comprises contacting a cell which expresses a membrane-bound form of FCTRX protein, or a biologically-active portion thereof, on the cell surface with a known compound which binds FCTRX to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with an FCTRX protein, wherein determining the ability of the test compound to interact with an FCTRX protein comprises determining the ability of the test compound to preferentially bind to FCTRX protein or a biologically-active portion thereof as compared to the known compound.

In another embodiment, an assay is a cell-based assay comprising contacting a cell expressing a membrane-bound form of FCTRX protein, or a biologically-active portion thereof, on the cell surface with a test compound and determining the ability of the test compound to modulate (*e.g.*, stimulate or inhibit) the activity of the FCTRX protein or biologically-active portion thereof. Determining the ability of the test compound to modulate the activity of FCTRX or a biologically-active portion thereof can be accomplished, for example, by determining the ability of the FCTRX protein to bind to or interact with an FCTRX target molecule. As used herein, a "target molecule" is a molecule with which an FCTRX protein

binds or interacts in nature, for example, a molecule on the surface of a cell which expresses an FCTRX interacting protein, a molecule on the surface of a second cell, a molecule in the extracellular milieu, a molecule associated with the internal surface of a cell membrane or a cytoplasmic molecule. An FCTRX target molecule can be a non-FCTRX molecule or an FCTRX protein or polypeptide of the invention . In one embodiment, an FCTRX target molecule is a component of a signal transduction pathway that facilitates transduction of an extracellular signal (*e.g.* a signal generated by binding of a compound to a membrane-bound FCTRX molecule) through the cell membrane and into the cell. The target, for example, can be a second intercellular protein that has catalytic activity or a protein that facilitates the association of downstream signaling molecules with FCTRX.

Determining the ability of the FCTRX protein to bind to or interact with an FCTRX target molecule can be accomplished by one of the methods described above for determining direct binding. In one embodiment, determining the ability of the FCTRX protein to bind to or interact with an FCTRX target molecule can be accomplished by determining the activity of the target molecule. For example, the activity of the target molecule can be determined by detecting induction of a cellular second messenger of the target (*i.e.* intracellular Ca^{2+}, diacylglycerol, IP_3, etc.), detecting catalytic/enzymatic activity of the target an appropriate substrate, detecting the induction of a reporter gene (comprising an FCTRX-responsive regulatory element operatively linked to a nucleic acid encoding a detectable marker, *e.g.*, luciferase), or detecting a cellular response, for example, cell survival, cellular differentiation, or cell proliferation.

In yet another embodiment, an assay of the invention is a cell-free assay comprising contacting an FCTRX protein or biologically-active portion thereof with a test compound and determining the ability of the test compound to bind to the FCTRX protein or biologically-active portion thereof. Binding of the test compound to the FCTRX protein can be determined either directly or indirectly as described above. In one such embodiment, the assay comprises contacting the FCTRX protein or biologically-active portion thereof with a known compound which binds FCTRX to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with an FCTRX protein, wherein determining the ability of the test compound to interact with an FCTRX protein comprises determining the ability of the test compound to preferentially bind to FCTRX or biologically-active portion thereof as compared to the known compound.

In still another embodiment, an assay is a cell-free assay comprising contacting FCTRX protein or biologically-active portion thereof with a test compound and determining the ability of the test compound to modulate (*e.g.* stimulate or inhibit) the activity of the FCTRX protein or biologically-active portion thereof. Determining the ability of the test compound to modulate

the activity of FCTRX can be accomplished, for example, by determining the ability of the FCTRX protein to bind to an FCTRX target molecule by one of the methods described above for determining direct binding. In an alternative embodiment, determining the ability of the test compound to modulate the activity of FCTRX protein can be accomplished by determining the ability of the FCTRX protein further modulate an FCTRX target molecule. For example, the catalytic/enzymatic activity of the target molecule on an appropriate substrate can be determined as described, *supra*.

In yet another embodiment, the cell-free assay comprises contacting the FCTRX protein or biologically-active portion thereof with a known compound which binds FCTRX protein to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with an FCTRX protein, wherein determining the ability of the test compound to interact with an FCTRX protein comprises determining the ability of the FCTRX protein to preferentially bind to or modulate the activity of an FCTRX target molecule.

The cell-free assays of the invention are amenable to use of both the soluble form or the membrane-bound form of FCTRX protein. In the case of cell-free assays comprising the membrane-bound form of FCTRX protein, it may be desirable to utilize a solubilizing agent such that the membrane-bound form of FCTRX protein is maintained in solution. Examples of such solubilizing agents include non-ionic detergents such as n-octylglucoside, n-dodecylglucoside, n-dodecylmaltoside, octanoyl-N-methylglucamide, decanoyl-N-methylglucamide, Triton® X-100, Triton® X-114, Thesit®, Isotridecypoly(ethylene glycol ether)$_n$, N-dodecyl--N,N-dimethyl-3-ammonio-1-propane sulfonate, 3-(3-cholamidopropyl) dimethylamminiol-1-propane sulfonate (CHAPS), or 3-(3-cholamidopropyl)dimethylamminiol-2-hydroxy-1-propane sulfonate (CHAPSO).

In more than one embodiment of the above assay methods of the invention, it may be desirable to immobilize either FCTRX protein or its target molecule to facilitate separation of complexed from uncomplexed forms of one or both of the proteins, as well as to accommodate automation of the assay. Binding of a test compound to FCTRX protein, or interaction of FCTRX protein with a target molecule in the presence and absence of a candidate compound, can be accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtiter plates, test tubes, and micro-centrifuge tubes. In one embodiment, a fusion protein can be provided that adds a domain that allows one or both of the proteins to be bound to a matrix. For example, GST-FCTRX fusion proteins or GST-target fusion proteins can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtiter plates, that are then combined with the test compound or the test compound and either the non-adsorbed target protein or FCTRX protein, and the mixture is

incubated under conditions conducive to complex formation (*e.g.*, at physiological conditions for salt and pH). Following incubation, the beads or microtiter plate wells are washed to remove any unbound components, the matrix immobilized in the case of beads, complex determined either directly or indirectly, for example, as described, *supra*. Alternatively, the complexes can be dissociated from the matrix, and the level of FCTRX protein binding or activity determined using standard techniques.

Other techniques for immobilizing proteins on matrices can also be used in the screening assays of the invention. For example, either the FCTRX protein or its target molecule can be immobilized utilizing conjugation of biotin and streptavidin. Biotinylated FCTRX protein or target molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques well-known within the art (*e.g.*, biotinylation kit, Pierce Chemicals, Rockford, Ill.), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). Alternatively, antibodies reactive with FCTRX protein or target molecules, but which do not interfere with binding of the FCTRX protein to its target molecule, can be derivatized to the wells of the plate, and unbound target or FCTRX protein trapped in the wells by antibody conjugation. Methods for detecting such complexes, in addition to those described above for the GST-immobilized complexes, include immunodetection of complexes using antibodies reactive with the FCTRX protein or target molecule, as well as enzyme-linked assays that rely on detecting an enzymatic activity associated with the FCTRX protein or target molecule.

In another embodiment, modulators of FCTRX protein expression are identified in a method wherein a cell is contacted with a candidate compound and the expression of FCTRX mRNA or protein in the cell is determined. The level of expression of FCTRX mRNA or protein in the presence of the candidate compound is compared to the level of expression of FCTRX mRNA or protein in the absence of the candidate compound. The candidate compound can then be identified as a modulator of FCTRX mRNA or protein expression based upon this comparison. For example, when expression of FCTRX mRNA or protein is greater (*i.e.*, statistically significantly greater) in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of FCTRX mRNA or protein expression. Alternatively, when expression of FCTRX mRNA or protein is less (statistically significantly less) in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of FCTRX mRNA or protein expression. The level of FCTRX mRNA or protein expression in the cells can be determined by methods described herein for detecting FCTRX mRNA or protein.

In yet another aspect of the invention, the FCTRX proteins can be used as "bait proteins" in a two-hybrid assay or three hybrid assay (*see, e.g.*, U.S. Patent No. 5,283,317; Zervos, *et al.*,

1993. *Cell* 72: 223-232; Madura, *et al.*, 1993. *J. Biol. Chem.* 268: 12046-12054; Bartel, *et al.*, 1993. *Biotechniques* 14: 920-924; Iwabuchi, *et al.*, 1993. *Oncogene* 8: 1693-1696; and Brent WO 94/10300), to identify other proteins that bind to or interact with FCTRX ("FCTRX-binding proteins" or "FCTRX-bp") and modulate FCTRX activity. Such FCTRX-binding proteins are also likely to be involved in the propagation of signals by the FCTRX proteins as, for example, upstream or downstream elements of the FCTRX pathway.

The two-hybrid system is based on the modular nature of most transcription factors, which consist of separable DNA-binding and activation domains. Briefly, the assay utilizes two different DNA constructs. In one construct, the gene that codes for FCTRX is fused to a gene encoding the DNA binding domain of a known transcription factor (*e.g.*, GAL-4). In the other construct, a DNA sequence, from a library of DNA sequences, that encodes an unidentified protein ("prey" or "sample") is fused to a gene that codes for the activation domain of the known transcription factor. If the "bait" and the "prey" proteins are able to interact, *in vivo*, forming an FCTRX-dependent complex, the DNA-binding and activation domains of the transcription factor are brought into close proximity. This proximity allows transcription of a reporter gene (*e.g.*, LacZ) that is operably linked to a transcriptional regulatory site responsive to the transcription factor. Expression of the reporter gene can be detected and cell colonies containing the functional transcription factor can be isolated and used to obtain the cloned gene that encodes the protein which interacts with FCTRX.

The invention further pertains to novel agents identified by the aforementioned screening assays and uses thereof for treatments as described herein.

Detection Assays

Portions or fragments of the cDNA sequences identified herein (and the corresponding complete gene sequences) can be used in numerous ways as polynucleotide reagents. By way of example, and not of limitation, these sequences can be used to: (*i*) map their respective genes on a chromosome; and, thus, locate gene regions associated with genetic disease; (*ii*) identify an individual from a minute biological sample (tissue typing); and (*iii*) aid in forensic identification of a biological sample. Some of these applications are described in the subsections, below.

Chromosome Mapping

Once the sequence (or a portion of the sequence) of a gene has been isolated, this sequence can be used to map the location of the gene on a chromosome. This process is called chromosome mapping. Accordingly, portions or fragments of the FCTRX sequences, SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29, or fragments or derivatives thereof, can be used to map the location of the FCTRX genes, respectively, on a chromosome. The

mapping of the FCTRX sequences to chromosomes is an important first step in correlating these sequences with genes associated with disease.

Briefly, FCTRX genes can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp in length) from the FCTRX sequences. Computer analysis of the FCTRX, sequences can be used to rapidly select primers that do not span more than one exon in the genomic DNA, thus complicating the amplification process. These primers can then be used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to the FCTRX sequences will yield an amplified fragment.

Somatic cell hybrids are prepared by fusing somatic cells from different mammals (*e.g.*, human and mouse cells). As hybrids of human and mouse cells grow and divide, they gradually lose human chromosomes in random order, but retain the mouse chromosomes. By using media in which mouse cells cannot grow, because they lack a particular enzyme, but in which human cells can, the one human chromosome that contains the gene encoding the needed enzyme will be retained. By using various media, panels of hybrid cell lines can be established. Each cell line in a panel contains either a single human chromosome or a small number of human chromosomes, and a full set of mouse chromosomes, allowing easy mapping of individual genes to specific human chromosomes. *See, e.g.,* D'Eustachio, *et al.*, 1983. *Science* 220: 919-924. Somatic cell hybrids containing only fragments of human chromosomes can also be produced by using human chromosomes with translocations and deletions.

PCR mapping of somatic cell hybrids is a rapid procedure for assigning a particular sequence to a particular chromosome. Three or more sequences can be assigned per day using a single thermal cycler. Using the FCTRX sequences to design oligonucleotide primers, sub-localization can be achieved with panels of fragments from specific chromosomes.

Fluorescence *in situ* hybridization (FISH) of a DNA sequence to a metaphase chromosomal spread can further be used to provide a precise chromosomal location in one step. Chromosome spreads can be made using cells whose division has been blocked in metaphase by a chemical like colcemid that disrupts the mitotic spindle. The chromosomes can be treated briefly with trypsin, and then stained with Giemsa. A pattern of light and dark bands develops on each chromosome, so that the chromosomes can be identified individually. The FISH technique can be used with a DNA sequence as short as 500 or 600 bases. However, clones larger than 1,000 bases have a higher likelihood of binding to a unique chromosomal location with sufficient signal intensity for simple detection. Preferably 1,000 bases, and more preferably 2,000 bases, will suffice to get good results at a reasonable amount of time. For a

review of this technique, *see,* Verma, *et al.*, HUMAN CHROMOSOMES: A MANUAL OF BASIC TECHNIQUES (Pergamon Press, New York 1988).

Reagents for chromosome mapping can be used individually to mark a single chromosome or a single site on that chromosome, or panels of reagents can be used for marking multiple sites and/or multiple chromosomes. Reagents corresponding to noncoding regions of the genes actually are preferred for mapping purposes. Coding sequences are more likely to be conserved within gene families, thus increasing the chance of cross hybridizations during chromosomal mapping.

Once a sequence has been mapped to a precise chromosomal location, the physical position of the sequence on the chromosome can be correlated with genetic map data. Such data are found, *e.g.,* in McKusick, MENDELIAN INHERITANCE IN MAN, available on-line through Johns Hopkins University Welch Medical Library). The relationship between genes and disease, mapped to the same chromosomal region, can then be identified through linkage analysis (co-inheritance of physically adjacent genes), described in, *e.g.,* Egeland, *et al.*, 1987. *Nature*, **325**: 783-787.

Moreover, differences in the DNA sequences between individuals affected and unaffected with a disease associated with the FCTRX gene, can be determined. If a mutation is observed in some or all of the affected individuals but not in any unaffected individuals, then the mutation is likely to be the causative agent of the particular disease. Comparison of affected and unaffected individuals generally involves first looking for structural alterations in the chromosomes, such as deletions or translocations that are visible from chromosome spreads or detectable using PCR based on that DNA sequence. Ultimately, complete sequencing of genes from several individuals can be performed to confirm the presence of a mutation and to distinguish mutations from polymorphisms.

Tissue Typing

The FCTRX sequences of the invention can also be used to identify individuals from minute biological samples. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identification. The sequences of the invention are useful as additional DNA markers for RFLP ("restriction fragment length polymorphisms," described in U.S. Patent No. 5,272,057).

Furthermore, the sequences of the invention can be used to provide an alternative technique that determines the actual base-by-base DNA sequence of selected portions of an individual's genome. Thus, the FCTRX sequences described herein can be used to prepare two PCR primers from the 5'- and 3'-termini of the sequences. These primers can then be used to amplify an individual's DNA and subsequently sequence it.

Panels of corresponding DNA sequences from individuals, prepared in this manner, can provide unique individual identifications, as each individual will have a unique set of such DNA sequences due to allelic differences. The sequences of the invention can be used to obtain such identification sequences from individuals and from tissue. The FCTRX sequences of the invention uniquely represent portions of the human genome. Allelic variation occurs to some degree in the coding regions of these sequences, and to a greater degree in the noncoding regions. It is estimated that allelic variation between individual humans occurs with a frequency of about once per each 500 bases. Much of the allelic variation is due to single nucleotide polymorphisms (SNPs), which include restriction fragment length polymorphisms (RFLPs).

Each of the sequences described herein can, to some degree, be used as a standard against which DNA from an individual can be compared for identification purposes. Because greater numbers of polymorphisms occur in the noncoding regions, fewer sequences are necessary to differentiate individuals. The noncoding sequences can comfortably provide positive individual identification with a panel of perhaps 10 to 1,000 primers that each yield a noncoding amplified sequence of 100 bases. If predicted coding sequences, such as those in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29, are used, a more appropriate number of primers for positive individual identification would be 500-2,000.

Predictive Medicine

The invention also pertains to the field of predictive medicine in which diagnostic assays, prognostic assays, pharmacogenomics, and monitoring clinical trials are used for prognostic (predictive) purposes to thereby treat an individual prophylactically. Accordingly, one aspect of the invention relates to diagnostic assays for determining FCTRX protein and/or nucleic acid expression as well as FCTRX activity, in the context of a biological sample (*e.g.*, blood, serum, cells, tissue) to thereby determine whether an individual is afflicted with a disease or disorder, or is at risk of developing a disorder, associated with aberrant FCTRX expression or activity. The disorders include metabolic disorders, diabetes, obesity, infectious disease, anorexia, cancer-associated cachexia, cancer, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, and hematopoietic disorders, and the various dyslipidemias, metabolic disturbances associated with obesity, the metabolic syndrome X and wasting disorders associated with chronic diseases and various cancers. The invention also provides for prognostic (or predictive) assays for determining whether an individual is at risk of developing a disorder associated with FCTRX protein, nucleic acid expression or activity. For example, mutations in an FCTRX gene can be assayed in a biological sample. Such assays can be used for prognostic or predictive purpose to thereby prophylactically treat an individual prior

to the onset of a disorder characterized by or associated with FCTRX protein, nucleic acid expression, or biological activity.

Another aspect of the invention provides methods for determining FCTRX protein, nucleic acid expression or activity in an individual to thereby select appropriate therapeutic or prophylactic agents for that individual (referred to herein as "pharmacogenomics"). Pharmacogenomics allows for the selection of agents (*e.g.*, drugs) for therapeutic or prophylactic treatment of an individual based on the genotype of the individual (*e.g.*, the genotype of the individual examined to determine the ability of the individual to respond to a particular agent.)

Yet another aspect of the invention pertains to monitoring the influence of agents (*e.g.*, drugs, compounds) on the expression or activity of FCTRX in clinical trials.

These and other agents are described in further detail in the following sections.

Diagnostic Assays

An exemplary method for detecting the presence or absence of FCTRX in a biological sample involves obtaining a biological sample from a test subject and contacting the biological sample with a compound or an agent capable of detecting FCTRX protein or nucleic acid (*e.g.*, mRNA, genomic DNA) that encodes FCTRX protein such that the presence of FCTRX is detected in the biological sample. An agent for detecting FCTRX mRNA or genomic DNA is a labeled nucleic acid probe capable of hybridizing to FCTRX mRNA or genomic DNA. The nucleic acid probe can be, for example, a full-length FCTRX nucleic acid, such as the nucleic acid of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29, or a portion thereof, such as an oligonucleotide of at least 15, 30, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to FCTRX mRNA or genomic DNA. Other suitable probes for use in the diagnostic assays of the invention are described herein.

An agent for detecting FCTRX protein is an antibody capable of binding to FCTRX protein, preferably an antibody with a detectable label. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment thereof (*e.g.*, Fab or $F(ab')_2$) can be used. The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (*i.e.*, physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently-labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently-labeled streptavidin. The term "biological sample" is intended to include tissues, cells and biological fluids isolated from a subject, as well as tissues, cells and fluids present within a subject. That is, the detection method

of the invention can be used to detect FCTRX mRNA, protein, or genomic DNA in a biological sample *in vitro* as well as *in vivo*. For example, *in vitro* techniques for detection of FCTRX mRNA include Northern hybridizations and *in situ* hybridizations. *In vitro* techniques for detection of FCTRX protein include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations, and immunofluorescence. *In vitro* techniques for detection of FCTRX genomic DNA include Southern hybridizations. Furthermore, *in vivo* techniques for detection of FCTRX protein include introducing into a subject a labeled anti-FCTRX antibody. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

In one embodiment, the biological sample contains protein molecules from the test subject. Alternatively, the biological sample can contain mRNA molecules from the test subject or genomic DNA molecules from the test subject. A preferred biological sample is a peripheral blood leukocyte sample isolated by conventional means from a subject.

In another embodiment, the methods further involve obtaining a control biological sample from a control subject, contacting the control sample with a compound or agent capable of detecting FCTRX protein, mRNA, or genomic DNA, such that the presence of FCTRX protein, mRNA or genomic DNA is detected in the biological sample, and comparing the presence of FCTRX protein, mRNA or genomic DNA in the control sample with the presence of FCTRX protein, mRNA or genomic DNA in the test sample.

The invention also encompasses kits for detecting the presence of FCTRX in a biological sample. For example, the kit can comprise: a labeled compound or agent capable of detecting FCTRX protein or mRNA in a biological sample; means for determining the amount of FCTRX in the sample; and means for comparing the amount of FCTRX in the sample with a standard. The compound or agent can be packaged in a suitable container. The kit can further comprise instructions for using the kit to detect FCTRX protein or nucleic acid.

Prognostic Assays

The diagnostic methods described herein can furthermore be utilized to identify subjects having or at risk of developing a disease or disorder associated with aberrant FCTRX expression or activity. For example, the assays described herein, such as the preceding diagnostic assays or the following assays, can be utilized to identify a subject having or at risk of developing a disorder associated with FCTRX protein, nucleic acid expression or activity. Alternatively, the prognostic assays can be utilized to identify a subject having or at risk for developing a disease or disorder. Thus, the invention provides a method for identifying a disease or disorder associated with aberrant FCTRX expression or activity in which a test sample is obtained from a subject and FCTRX protein or nucleic acid (*e.g.*, mRNA, genomic DNA) is detected, wherein

the presence of FCTRX protein or nucleic acid is diagnostic for a subject having or at risk of developing a disease or disorder associated with aberrant FCTRX expression or activity. As used herein, a "test sample" refers to a biological sample obtained from a subject of interest. For example, a test sample can be a biological fluid (*e.g.*, serum), cell sample, or tissue.

Furthermore, the prognostic assays described herein can be used to determine whether a subject can be administered an agent (*e.g.*, an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug candidate) to treat a disease or disorder associated with aberrant FCTRX expression or activity. For example, such methods can be used to determine whether a subject can be effectively treated with an agent for a disorder. Thus, the invention provides methods for determining whether a subject can be effectively treated with an agent for a disorder associated with aberrant FCTRX expression or activity in which a test sample is obtained and FCTRX protein or nucleic acid is detected (*e.g.*, wherein the presence of FCTRX protein or nucleic acid is diagnostic for a subject that can be administered the agent to treat a disorder associated with aberrant FCTRX expression or activity).

The methods of the invention can also be used to detect genetic lesions in an FCTRX gene, thereby determining if a subject with the lesioned gene is at risk for a disorder characterized by aberrant cell proliferation and/or differentiation. In various embodiments, the methods include detecting, in a sample of cells from the subject, the presence or absence of a genetic lesion characterized by at least one of an alteration affecting the integrity of a gene encoding an FCTRX-protein, or the misexpression of the FCTRX gene. For example, such genetic lesions can be detected by ascertaining the existence of at least one of: (*i*) a deletion of one or more nucleotides from an FCTRX gene; (*ii*) an addition of one or more nucleotides to an FCTRX gene; (*iii*) a substitution of one or more nucleotides of an FCTRX gene, (*iv*) a chromosomal rearrangement of an FCTRX gene; (*v*) an alteration in the level of a messenger RNA transcript of an FCTRX gene, (*vi*) aberrant modification of an FCTRX gene, such as of the methylation pattern of the genomic DNA, (*vii*) the presence of a non-wild-type splicing pattern of a messenger RNA transcript of an FCTRX gene, (*viii*) a non-wild-type level of an FCTRX protein, (*ix*) allelic loss of an FCTRX gene, and (*x*) inappropriate post-translational modification of an FCTRX protein. As described herein, there are a large number of assay techniques known in the art which can be used for detecting lesions in an FCTRX gene. A preferred biological sample is a peripheral blood leukocyte sample isolated by conventional means from a subject. However, any biological sample containing nucleated cells may be used, including, for example, buccal mucosal cells.

In certain embodiments, detection of the lesion involves the use of a probe/primer in a polymerase chain reaction (PCR) (*see, e.g.*, U.S. Patent Nos. 4,683,195 and 4,683,202), such as

anchor PCR or RACE PCR, or, alternatively, in a ligation chain reaction (LCR) (*see, e.g.*, Landegran, *et al.*, 1988. *Science* 241: 1077-1080; and Nakazawa, *et al.*, 1994. *Proc. Natl. Acad. Sci. USA* 91: 360-364), the latter of which can be particularly useful for detecting point mutations in the FCTRX-gene (*see,* Abravaya, *et al.*, 1995. *Nucl. Acids Res.* 23: 675-682). This method can include the steps of collecting a sample of cells from a patient, isolating nucleic acid (*e.g.*, genomic, mRNA or both) from the cells of the sample, contacting the nucleic acid sample with one or more primers that specifically hybridize to an FCTRX gene under conditions such that hybridization and amplification of the FCTRX gene (if present) occurs, and detecting the presence or absence of an amplification product, or detecting the size of the amplification product and comparing the length to a control sample. It is anticipated that PCR and/or LCR may be desirable to use as a preliminary amplification step in conjunction with any of the techniques used for detecting mutations described herein.

Alternative amplification methods include: self sustained sequence replication (*see,* Guatelli, *et al.*, 1990. *Proc. Natl. Acad. Sci. USA* 87: 1874-1878), transcriptional amplification system (*see,* Kwoh, *et al.*, 1989. *Proc. Natl. Acad. Sci. USA* 86: 1173-1177); Qβ Replicase (*see,* Lizardi, *et al*, 1988. *BioTechnology* 6: 1197), or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers.

In an alternative embodiment, mutations in an FCTRX gene from a sample cell can be identified by alterations in restriction enzyme cleavage patterns. For example, sample and control DNA is isolated, amplified (optionally), digested with one or more restriction endonucleases, and fragment length sizes are determined by gel electrophoresis and compared. Differences in fragment length sizes between sample and control DNA indicates mutations in the sample DNA. Moreover, the use of sequence specific ribozymes (*see, e.g.,* U.S. Patent No. 5,493,531) can be used to score for the presence of specific mutations by development or loss of a ribozyme cleavage site.

In other embodiments, genetic mutations in FCTRX can be identified by hybridizing a sample and control nucleic acids, *e.g.*, DNA or RNA, to high-density arrays containing hundreds or thousands of oligonucleotides probes. *See, e.g.,* Cronin, *et al.*, 1996. *Human Mutation* 7: 244-255; Kozal, *et al.*, 1996. *Nat. Med.* 2: 753-759. For example, genetic mutations in FCTRX can be identified in two dimensional arrays containing light-generated DNA probes as described in Cronin, *et al.*, *supra.* Briefly, a first hybridization array of probes can be used to scan through long stretches of DNA in a sample and control to identify base changes between the sequences by making linear arrays of sequential overlapping probes. This step allows the identification of

point mutations. This is followed by a second hybridization array that allows the characterization of specific mutations by using smaller, specialized probe arrays complementary to all variants or mutations detected. Each mutation array is composed of parallel probe sets, one complementary to the wild-type gene and the other complementary to the mutant gene.

In yet another embodiment, any of a variety of sequencing reactions known in the art can be used to directly sequence the FCTRX gene and detect mutations by comparing the sequence of the sample FCTRX with the corresponding wild-type (control) sequence. Examples of sequencing reactions include those based on techniques developed by Maxim and Gilbert, 1977. *Proc. Natl. Acad. Sci. USA* 74: 560 or Sanger, 1977. *Proc. Natl. Acad. Sci. USA* 74: 5463. It is also contemplated that any of a variety of automated sequencing procedures can be utilized when performing the diagnostic assays (*see, e.g.,* Naeve, *et al.*, 1995. *Biotechniques* 19: 448), including sequencing by mass spectrometry (see, *e.g.*, PCT International Publication No. WO 94/16101; Cohen, *et al.*, 1996. *Adv. Chromatography* 36: 127-162; and Griffin, *et al.*, 1993. *Appl. Biochem. Biotechnol.* 38: 147-159).

Other methods for detecting mutations in the FCTRX gene include methods in which protection from cleavage agents is used to detect mismatched bases in RNA/RNA or RNA/DNA heteroduplexes. *See, e.g.,* Myers, *et al.*, 1985. *Science* 230: 1242. In general, the art technique of "mismatch cleavage" starts by providing heteroduplexes of formed by hybridizing (labeled) RNA or DNA containing the wild-type FCTRX sequence with potentially mutant RNA or DNA obtained from a tissue sample. The double-stranded duplexes are treated with an agent that cleaves single-stranded regions of the duplex such as which will exist due to basepair mismatches between the control and sample strands. For instance, RNA/DNA duplexes can be treated with RNase and DNA/DNA hybrids treated with S_1 nuclease to enzymatically digesting the mismatched regions. In other embodiments, either DNA/DNA or RNA/DNA duplexes can be treated with hydroxylamine or osmium tetroxide and with piperidine in order to digest mismatched regions. After digestion of the mismatched regions, the resulting material is then separated by size on denaturing polyacrylamide gels to determine the site of mutation. *See, e.g.,* Cotton, *et al.,* 1988. *Proc. Natl. Acad. Sci. USA* 85: 4397; Saleeba, *et al.,* 1992. *Methods Enzymol.* 217: 286-295. In an embodiment, the control DNA or RNA can be labeled for detection.

In still another embodiment, the mismatch cleavage reaction employs one or more proteins that recognize mismatched base pairs in double-stranded DNA (so called "DNA mismatch repair" enzymes) in defined systems for detecting and mapping point mutations in FCTRX cDNAs obtained from samples of cells. For example, the mutY enzyme of *E. coli* cleaves A at G/A mismatches and the thymidine DNA glycosylase from HeLa cells cleaves T at

G/T mismatches. *See, e.g.,* Hsu, *et al.*, 1994. *Carcinogenesis* 15: 1657-1662. According to an exemplary embodiment, a probe based on an FCTRX sequence, *e.g.*, a wild-type FCTRX sequence, is hybridized to a cDNA or other DNA product from a test cell(s). The duplex is treated with a DNA mismatch repair enzyme, and the cleavage products, if any, can be detected from electrophoresis protocols or the like. *See, e.g.,* U.S. Patent No. 5,459,039.

In other embodiments, alterations in electrophoretic mobility will be used to identify mutations in FCTRX genes. For example, single strand conformation polymorphism (SSCP) may be used to detect differences in electrophoretic mobility between mutant and wild type nucleic acids. *See, e.g.,* Orita, *et al.*, 1989. *Proc. Natl. Acad. Sci. USA*: 86: 2766; Cotton, 1993. *Mutat. Res.* 285: 125-144; Hayashi, 1992. *Genet. Anal. Tech. Appl.* 9: 73-79. Single-stranded DNA fragments of sample and control FCTRX nucleic acids will be denatured and allowed to renature. The secondary structure of single-stranded nucleic acids varies according to sequence, the resulting alteration in electrophoretic mobility enables the detection of even a single base change. The DNA fragments may be labeled or detected with labeled probes. The sensitivity of the assay may be enhanced by using RNA (rather than DNA), in which the secondary structure is more sensitive to a change in sequence. In one embodiment, the subject method utilizes heteroduplex analysis to separate double stranded heteroduplex molecules on the basis of changes in electrophoretic mobility. *See, e.g.,* Keen, *et al.*, 1991. *Trends Genet.* 7: 5.

In yet another embodiment, the movement of mutant or wild-type fragments in polyacrylamide gels containing a gradient of denaturant is assayed using denaturing gradient gel electrophoresis (DGGE). *See, e.g.,* Myers, *et al.*, 1985. *Nature* 313: 495. When DGGE is used as the method of analysis, DNA will be modified to insure that it does not completely denature, for example by adding a GC clamp of approximately 40 bp of high-melting GC-rich DNA by PCR. In a further embodiment, a temperature gradient is used in place of a denaturing gradient to identify differences in the mobility of control and sample DNA. *See, e.g.,* Rosenbaum and Reissner, 1987. *Biophys. Chem.* 265: 12753.

Examples of other techniques for detecting point mutations include, but are not limited to, selective oligonucleotide hybridization, selective amplification, or selective primer extension. For example, oligonucleotide primers may be prepared in which the known mutation is placed centrally and then hybridized to target DNA under conditions that permit hybridization only if a perfect match is found. *See, e.g.,* Saiki, *et al.*, 1986. *Nature* 324: 163; Saiki, *et al.*, 1989. *Proc. Natl. Acad. Sci. USA* 86: 6230. Such allele specific oligonucleotides are hybridized to PCR amplified target DNA or a number of different mutations when the oligonucleotides are attached to the hybridizing membrane and hybridized with labeled target DNA.

Alternatively, allele specific amplification technology that depends on selective PCR amplification may be used in conjunction with the instant invention. Oligonucleotides used as primers for specific amplification may carry the mutation of interest in the center of the molecule (so that amplification depends on differential hybridization; *see, e.g.,* Gibbs, *et al.,* 1989. *Nucl. Acids Res.* 17: 2437-2448) or at the extreme 3'-terminus of one primer where, under appropriate conditions, mismatch can prevent, or reduce polymerase extension (*see, e.g.,* Prossner, 1993. *Tibtech.* 11: 238). In addition it may be desirable to introduce a novel restriction site in the region of the mutation to create cleavage-based detection. *See, e.g.,* Gasparini, *et al.,* 1992. *Mol. Cell Probes* 6: 1. It is anticipated that in certain embodiments amplification may also be performed using *Taq* ligase for amplification. *See, e.g.,* Barany, 1991. *Proc. Natl. Acad. Sci. USA* 88: 189. In such cases, ligation will occur only if there is a perfect match at the 3'-terminus of the 5' sequence, making it possible to detect the presence of a known mutation at a specific site by looking for the presence or absence of amplification.

The methods described herein may be performed, for example, by utilizing pre-packaged diagnostic kits comprising at least one probe nucleic acid or antibody reagent described herein, which may be conveniently used, *e.g.,* in clinical settings to diagnose patients exhibiting symptoms or family history of a disease or illness involving an FCTRX gene.

Furthermore, any cell type or tissue, preferably peripheral blood leukocytes, in which FCTRX is expressed may be utilized in the prognostic assays described herein. However, any biological sample containing nucleated cells may be used, including, for example, buccal mucosal cells.

Pharmacogenomics

Agents, or modulators that have a stimulatory or inhibitory effect on FCTRX activity (*e.g.,* FCTRX gene expression), as identified by a screening assay described herein can be administered to individuals to treat (prophylactically or therapeutically) disorders (The disorders include metabolic disorders, diabetes, obesity, infectious disease, anorexia, cancer-associated cachexia, cancer, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, and hematopoietic disorders, and the various dyslipidemias, metabolic disturbances associated with obesity, the metabolic syndrome X and wasting disorders associated with chronic diseases and various cancers.) In conjunction with such treatment, the pharmacogenomics (*i.e.,* the study of the relationship between an individual's genotype and that individual's response to a foreign compound or drug) of the individual may be considered. Differences in metabolism of therapeutics can lead to severe toxicity or therapeutic failure by altering the relation between dose and blood concentration of the pharmacologically active drug. Thus, the pharmacogenomics of the individual permits the selection of effective agents (*e.g.,*

drugs) for prophylactic or therapeutic treatments based on a consideration of the individual's genotype. Such pharmacogenomics can further be used to determine appropriate dosages and therapeutic regimens. Accordingly, the activity of FCTRX protein, expression of FCTRX nucleic acid, or mutation content of FCTRX genes in an individual can be determined to thereby select appropriate agent(s) for therapeutic or prophylactic treatment of the individual.

Pharmacogenomics deals with clinically significant hereditary variations in the response to drugs due to altered drug disposition and abnormal action in affected persons. See *e.g.*, Eichelbaum, 1996. *Clin. Exp. Pharmacol. Physiol.*, 23: 983-985; Linder, 1997. *Clin. Chem.*, 43: 254-266. In general, two types of pharmacogenetic conditions can be differentiated. Genetic conditions transmitted as a single factor altering the way drugs act on the body (altered drug action) or genetic conditions transmitted as single factors altering the way the body acts on drugs (altered drug metabolism). These pharmacogenetic conditions can occur either as rare defects or as polymorphisms. For example, glucose-6-phosphate dehydrogenase (G6PD) deficiency is a common inherited enzymopathy in which the main clinical complication is hemolysis after ingestion of oxidant drugs (anti-malarials, sulfonamides, analgesics, nitrofurans) and consumption of fava beans.

As an illustrative embodiment, the activity of drug metabolizing enzymes is a major determinant of both the intensity and duration of drug action. The discovery of genetic polymorphisms of drug metabolizing enzymes (*e.g.*, N-acetyltransferase 2 (NAT 2) and cytochrome P450 enzymes CYP2D6 and CYP2C19) has provided an explanation as to why some patients do not obtain the expected drug effects or show exaggerated drug response and serious toxicity after taking the standard and safe dose of a drug. These polymorphisms are expressed in two phenotypes in the population, the extensive metabolizer (EM) and poor metabolizer (PM). The prevalence of PM is different among different populations. For example, the gene coding for CYP2D6 is highly polymorphic and several mutations have been identified in PM, which all lead to the absence of functional CYP2D6. Poor metabolizers of CYP2D6 and CYP2C19 quite frequently experience exaggerated drug response and side effects when they receive standard doses. If a metabolite is the active therapeutic moiety, PM show no therapeutic response, as demonstrated for the analgesic effect of codeine mediated by its CYP2D6-formed metabolite morphine. At the other extreme are the so called ultra-rapid metabolizers who do not respond to standard doses. Recently, the molecular basis of ultra-rapid metabolism has been identified to be due to CYP2D6 gene amplification.

Thus, the activity of FCTRX protein, expression of FCTRX nucleic acid, or mutation content of FCTRX genes in an individual can be determined to thereby select appropriate agent(s) for therapeutic or prophylactic treatment of the individual. In addition,

pharmacogenetic studies can be used to apply genotyping of polymorphic alleles encoding drug-metabolizing enzymes to the identification of an individual's drug responsiveness phenotype. This knowledge, when applied to dosing or drug selection, can avoid adverse reactions or therapeutic failure and thus enhance therapeutic or prophylactic efficiency when treating a subject with an FCTRX modulator, such as a modulator identified by one of the exemplary screening assays described herein.

Monitoring of Effects During Clinical Trials

Monitoring the influence of agents (*e.g.*, drugs, compounds) on the expression or activity of FCTRX (*e.g.*, the ability to modulate aberrant cell proliferation and/or differentiation) can be applied not only in basic drug screening, but also in clinical trials. For example, the effectiveness of an agent determined by a screening assay as described herein to increase FCTRX gene expression, protein levels, or upregulate FCTRX activity, can be monitored in clinical trails of subjects exhibiting decreased FCTRX gene expression, protein levels, or downregulated FCTRX activity. Alternatively, the effectiveness of an agent determined by a screening assay to decrease FCTRX gene expression, protein levels, or downregulate FCTRX activity, can be monitored in clinical trails of subjects exhibiting increased FCTRX gene expression, protein levels, or upregulated FCTRX activity. In such clinical trials, the expression or activity of FCTRX and, preferably, other genes that have been implicated in, for example, a cellular proliferation or immune disorder can be used as a "read out" or markers of the immune responsiveness of a particular cell.

By way of example, and not of limitation, genes, including FCTRX, that are modulated in cells by treatment with an agent (*e.g.*, compound, drug or small molecule) that modulates FCTRX activity (*e.g.*, identified in a screening assay as described herein) can be identified. Thus, to study the effect of agents on cellular proliferation disorders, for example, in a clinical trial, cells can be isolated and RNA prepared and analyzed for the levels of expression of FCTRX and other genes implicated in the disorder. The levels of gene expression (*i.e.*, a gene expression pattern) can be quantified by Northern blot analysis or RT-PCR, as described herein, or alternatively by measuring the amount of protein produced, by one of the methods as described herein, or by measuring the levels of activity of FCTRX or other genes. In this manner, the gene expression pattern can serve as a marker, indicative of the physiological response of the cells to the agent. Accordingly, this response state may be determined before, and at various points during, treatment of the individual with the agent.

In one embodiment, the invention provides a method for monitoring the effectiveness of treatment of a subject with an agent (*e.g.*, an agonist, antagonist, protein, peptide, peptidomimetic, nucleic acid, small molecule, or other drug candidate identified by the

screening assays described herein) comprising the steps of (*i*) obtaining a pre-administration sample from a subject prior to administration of the agent; (*ii*) detecting the level of expression of an FCTRX protein, mRNA, or genomic DNA in the preadministration sample; (*iii*) obtaining one or more post-administration samples from the subject; (*iv*) detecting the level of expression or activity of the FCTRX protein, mRNA, or genomic DNA in the post-administration samples; (*v*) comparing the level of expression or activity of the FCTRX protein, mRNA, or genomic DNA in the pre-administration sample with the FCTRX protein, mRNA, or genomic DNA in the post administration sample or samples; and (*vi*) altering the administration of the agent to the subject accordingly. For example, increased administration of the agent may be desirable to increase the expression or activity of FCTRX to higher levels than detected, *i.e.*, to increase the effectiveness of the agent. Alternatively, decreased administration of the agent may be desirable to decrease expression or activity of FCTRX to lower levels than detected, *i.e.*, to decrease the effectiveness of the agent.

Methods of Treatment

The invention provides for both prophylactic and therapeutic methods of treating a subject at risk of (or susceptible to) a disorder or having a disorder associated with aberrant FCTRX expression or activity. The disorders include metabolic disorders, diabetes, obesity, infectious disease, anorexia, cancer-associated cachexia, cancer, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, and hematopoietic disorders, and the various dyslipidemias, metabolic disturbances associated with obesity, the metabolic syndrome X and wasting disorders associated with chronic diseases and various cancers. These methods of treatment will be discussed more fully, below.

Disease and Disorders

Diseases and disorders that are characterized by increased (relative to a subject not suffering from the disease or disorder) levels or biological activity may be treated with Therapeutics that antagonize (*i.e.*, reduce or inhibit) activity. Therapeutics that antagonize activity may be administered in a therapeutic or prophylactic manner. Therapeutics that may be utilized include, but are not limited to: (*i*) an aforementioned peptide, or analogs, derivatives, fragments or homologs thereof; (*ii*) antibodies to an aforementioned peptide; (*iii*) nucleic acids encoding an aforementioned peptide; (*iv*) administration of antisense nucleic acid and nucleic acids that are "dysfunctional" (*i.e.*, due to a heterologous insertion within the coding sequences of coding sequences to an aforementioned peptide) that are utilized to "knockout" endoggenous function of an aforementioned peptide by homologous recombination (*see, e.g.*, Capecchi, 1989. *Science* 244: 1288-1292); or (*v*) modulators (*i.e.*, inhibitors, agonists and antagonists, including

additional peptide mimetic of the invention or antibodies specific to a peptide of the invention) that alter the interaction between an aforementioned peptide and its binding partner.

Diseases and disorders that are characterized by decreased (relative to a subject not suffering from the disease or disorder) levels or biological activity may be treated with Therapeutics that increase (*i.e.*, are agonists to) activity. Therapeutics that upregulate activity may be administered in a therapeutic or prophylactic manner. Therapeutics that may be utilized include, but are not limited to, an aforementioned peptide, or analogs, derivatives, fragments or homologs thereof; or an agonist that increases bioavailability.

Increased or decreased levels can be readily detected by quantifying peptide and/or RNA, by obtaining a patient tissue sample (*e.g.*, from biopsy tissue) and assaying it *in vitro* for RNA or peptide levels, structure and/or activity of the expressed peptides (or mRNAs of an aforementioned peptide). Methods that are well-known within the art include, but are not limited to, immunoassays (*e.g.*, by Western blot analysis, immunoprecipitation followed by sodium dodecyl sulfate (SDS) polyacrylamide gel electrophoresis, immunocytochemistry, etc.) and/or hybridization assays to detect expression of mRNAs (*e.g.*, Northern assays, dot blots, *in situ* hybridization, and the like).

Prophylactic Methods

In one aspect, the invention provides a method for preventing, in a subject, a disease or condition associated with an aberrant FCTRX expression or activity, by administering to the subject an agent that modulates FCTRX expression or at least one FCTRX activity. Subjects at risk for a disease that is caused or contributed to by aberrant FCTRX expression or activity can be identified by, for example, any or a combination of diagnostic or prognostic assays as described herein. Administration of a prophylactic agent can occur prior to the manifestation of symptoms characteristic of the FCTRX aberrancy, such that a disease or disorder is prevented or, alternatively, delayed in its progression. Depending upon the type of FCTRX aberrancy, for example, an FCTRX agonist or FCTRX antagonist agent can be used for treating the subject. The appropriate agent can be determined based on screening assays described herein. The prophylactic methods of the invention are further discussed in the following subsections.

Therapeutic Methods

Another aspect of the invention pertains to methods of modulating FCTRX expression or activity for therapeutic purposes. The modulatory method of the invention involves contacting a cell with an agent that modulates one or more of the activities of FCTRX protein activity associated with the cell. An agent that modulates FCTRX protein activity can be an agent as described herein, such as a nucleic acid or a protein, a naturally-occurring cognate ligand of an FCTRX protein, a peptide, an FCTRX peptidomimetic, or other small molecule. In one

embodiment, the agent stimulates one or more FCTRX protein activity. Examples of such stimulatory agents include active FCTRX protein and a nucleic acid molecule encoding FCTRX that has been introduced into the cell. In another embodiment, the agent inhibits one or more FCTRX protein activity. Examples of such inhibitory agents include antisense FCTRX nucleic acid molecules and anti-FCTRX antibodies. These modulatory methods can be performed *in vitro* (*e.g.*, by culturing the cell with the agent) or, alternatively, *in vivo* (*e.g.*, by administering the agent to a subject). As such, the invention provides methods of treating an individual afflicted with a disease or disorder characterized by aberrant expression or activity of an FCTRX protein or nucleic acid molecule. In one embodiment, the method involves administering an agent (*e.g.*, an agent identified by a screening assay described herein), or combination of agents that modulates (*e.g.*, up-regulates or down-regulates) FCTRX expression or activity. In another embodiment, the method involves administering an FCTRX protein or nucleic acid molecule as therapy to compensate for reduced or aberrant FCTRX expression or activity.

Stimulation of FCTRX activity is desirable in situations in which FCTRX is abnormally downregulated and/or in which increased FCTRX activity is likely to have a beneficial effect. One example of such a situation is where a subject has a disorder characterized by aberrant cell proliferation and/or differentiation (*e.g.*, cancer or immune associated disorders). Another example of such a situation is where the subject has a gestational disease (*e.g.*, preclampsia).

Determination of the Biological Effect of the Therapeutic

In various embodiments of the invention, suitable *in vitro* or *in vivo* assays are performed to determine the effect of a specific Therapeutic and whether its administration is indicated for treatment of the affected tissue.

In various specific embodiments, *in vitro* assays may be performed with representative cells of the type(s) involved in the patient's disorder, to determine if a given Therapeutic exerts the desired effect upon the cell type(s). Compounds for use in therapy may be tested in suitable animal model systems including, but not limited to rats, mice, chicken, cows, monkeys, rabbits, and the like, prior to testing in human subjects. Similarly, for *in vivo* testing, any of the animal model system known in the art may be used prior to administration to human subjects.

Prophylactic and Therapeutic Uses of the Compositions of the Invention

The FCTRX nucleic acids and proteins of the invention are useful in potential prophylactic and therapeutic applications implicated in a variety of disorders including, but not limited to: metabolic disorders, diabetes, obesity, infectious disease, anorexia, cancer-associated cancer, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, hematopoietic disorders, and the various dyslipidemias, metabolic disturbances

associated with obesity, the metabolic syndrome X and wasting disorders associated with chronic diseases and various cancers.

As an example, a cDNA encoding the FCTRX protein of the invention may be useful in gene therapy, and the protein may be useful when administered to a subject in need thereof. By way of non-limiting example, the compositions of the invention will have efficacy for treatment of patients suffering from: metabolic disorders, diabetes, obesity, infectious disease, anorexia, cancer-associated cachexia, cancer, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, hematopoietic disorders, and the various dyslipidemias.

Both the novel nucleic acid encoding the FCTRX protein, and the FCTRX protein of the invention, or fragments thereof, may also be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed. A further use could be as an anti-bacterial molecule (*i.e.,* some peptides have been found to possess anti-bacterial properties). These materials are further useful in the generation of antibodies which immunospecifically-bind to the novel substances of the invention for use in therapeutic or diagnostic methods.

EXAMPLES

The following examples illustrate by way of non-limiting example various aspects of the invention.

Example 1: Method of Identifying the Nucleic Acids

The novel nucleic acids of the invention were identified by TblastN using CuraGen Corporation's sequence file, run against the Genomic Daily Files made available by GenBank. The nucleic acids were further predicted by the program GenScan™, including selection of exons. These were further modified by means of similarities using BLAST searches. The sequences were then manually corrected for apparent inconsistencies, thereby obtaining the sequences encoding the full-length proteins.

Example 2. Quantitative expression analysis of FCTR2 in various cells and tissues

The quantitative expression of clone AL078594_A (FCTR2) was assessed in a large number of normal and tumor sample cells and cell lines (Panel 1), as well as in surgical tissue samples (Panel 2), by real time quantitative PCR (TAQMAN®) performed on a Perkin-Elmer Biosystems ABI PRISM® 7700 Sequence Detection System.

First, 96 RNA samples were normalized to β-actin and GAPDH. RNA (~50 ng total or ~1 ng polyA+) was converted to cDNA using the TAQMAN® Reverse Transcription Reagents Kit (PE Biosystems, Foster City, CA; Catalog No. N808-0234) and random hexamers according to the manufacturer's protocol. Reactions were performed in 20 ul and incubated for 30 min. at 48°C. cDNA (5 ul) was then transferred to a separate plate for the TAQMAN® reaction using - actin and GAPDH TAQMAN® Assay Reagents (PE Biosystems; Catalog Nos. 4310881E and 4310884E, respectively) and TAQMAN® universal PCR Master Mix (PE Biosystems; Catalog No. 4304447) according to the manufacturer's protocol. Reactions were performed in 25 ul using the following parameters: 2 min. at 50°C; 10 min. at 95°C; 15 sec. at 95°C/1 min. at 60°C (40 cycles). Results were recorded as CT values (cycle at which a given sample crosses a threshold level of fluorescence) using a log scale, with the difference in RNA concentration between a given sample and the sample with the lowest CT value being represented as 2 to the power of delta CT. The percent relative expression is then obtained by taking the reciprocal of this RNA difference and multiplying by 100. The average CT values obtained for ß-actin and GAPDH were used to normalize RNA samples. The RNA sample generating the highest CT value required no further diluting, while all other samples were diluted relative to this sample according to their β-actin /GAPDH average CT values.

Normalized RNA (5 ul) was converted to cDNA and analyzed via TAQMAN® using One Step RT-PCR Master Mix Reagents (PE Biosystems; Catalog No. 4309169) and gene-specific primers according to the manufacturer's instructions. Probes and primers were designed for each assay according to Perkin Elmer Biosystem's *Primer Express* Software package (version I for Apple Computer's Macintosh Power PC) or a similar algorithm using the target sequence as input. Default settings were used for reaction conditions and the following parameters were set before selecting primers: primer concentration = 250 nM, primer melting temperature (T_m) range = 58°-60° C, primer optimal Tm = 59° C, maximum primer difference = 2° C, probe does not have 5' G, probe T_m must be 10° C greater than primer T_m, amplicon size 75 bp to 100 bp. The probes and primers selected (see below) were synthesized by Synthegen (Houston, TX, USA). Probes were double purified by HPLC to remove uncoupled dye and evaluated by mass spectroscopy to verify coupling of reporter and quencher dyes to the 5' and 3' ends of the probe, respectively. Their final concentrations were: forward and reverse primers, 900 nM each, and probe, 200nM.

The expression was probed with the primer-probe set Ag 259. The Forward primer sequence is 5'-GGAGAGGCTCTGAAGCTACACAA-3' (SEQ ID NO:31); the Probe primer sequence is TET-5'-TCAGCTGCACAAGCCCCCTGCT-3'-TAMRA (SEQ ID NO:32); and the

Reverse primer sequence is 5'-GCAGTGGTTGGAGCTGGAA-3' (SEQ ID NO:33). Table 15 shows the primer locations within the FCTR2 nucleic acid sequence.

Table 15. Primer-Probe Set Ag259

Primers	Length	Start Position
Forward	23	124
Probe	22	158
Reverse	19	181

PCR conditions: Normalized RNA from each tissue and each cell line was spotted in each well of a 96 well PCR plate (Perkin Elmer Biosystems). PCR cocktails including two probes (a probe specific for the target clone and another gene-specific probe multiplexed with the target probe) were set up using 1X TaqMan™ PCR Master Mix for the PE Biosystems 7700, with 5 mM MgCl2, dNTPs (dA, G, C, U at 1:1:1:2 ratios), 0.25 U/ml AmpliTaq Gold™ (PE Biosystems), and 0.4 U/μl RNase inhibitor, and 0.25 U/μl reverse transcriptase. Reverse transcription was performed at 48° C for 30 minutes followed by amplification/PCR cycles as follows: 95° C 10 min, then 40 cycles of 95° C for 15 seconds, 60° C for 1 minute.

The results for various cells and cell lines that constitute Panel 1 are shown in Table 16. In Table 16, the following abbreviations are used: ca. = carcinoma; * = established from metastasis; met = metastasis; s cell var= small cell variant; non-s = non-sm =non-small; squam = squamous; pl. eff = pl effusion = pleural effusion; glio = glioma; astro = astrocytoma; and neuro = neuroblastoma.

Table 16.

Tissue Name	**Rel. Expr., %**	**Tissue Name**	**Rel. Expr., %**
Adipose	100.0	Colon ca. HT29	0.2
Adrenal gland	0.0	Colon ca. CaCo-2	0.0
Bladder	0.2	Colon ca. HCT-15	3.0
Bone marrow	0.0	Colon ca. HCT-116	0.0
Endothelial cells	0.0	Colon ca. HCC-2998	0.2
Endothelial cells (treated)	0.0	Colon ca. SW480	1.5
Liver	1.5	Colon ca.* (SW480 met)SW620	0.0
Liver (fetal)	0.0	Fetal Skeletal	0.3
Spleen	0.0	Skeletal muscle	2.6
Thymus	0.0	Heart	6.4
Thyroid	0.0	Stomach	0.0
Trachea	0.0	Gastric ca.* (liver met) NCI-N87	0.3
Testis	0.1	Kidney	4.0
Spinal cord	0.6	Kidney (fetal)	0.1
Salavary gland	0.0	Renal ca. 786-0	0.0

Brain (amygdala)	0.0	Renal ca. A498	0.1
Brain (cerebellum)	2.9	Renal ca. ACHN	0.0
Brain (hippocampus)	0.0	Renal ca. TK-10	0.1
Brain (substantia nigra)	4.8	Renal ca. UO-31	0.1
Brain (thalamus)	0.1	Renal ca. RXF 393	0.0
Cerebral Cortex	0.0	Pancreas	1.5
Brain (whole)	0.0	Pancreatic ca. CAPAN 2	0.2
Brain (fetal)	0.0	Ovary	0.2
CNS ca. (glio/astro) U-118-MG	0.2	Ovarian ca. IGROV-1	0.7
CNS ca. (astro) SF-539	0.0	Ovarian ca. OVCAR-3	51.1
CNS ca. (astro) SNB-75	0.0	Ovarian ca. OVCAR-4	52.9
CNS ca. (astro) SW1783	0.0	Ovarian ca. OVCAR-5	21.6
CNS ca. (glio) U251	0.2	Ovarian ca. OVCAR-8	0.2
CNS ca. (glio) SF-295	0.0	Ovarian ca.* (ascites) SK-OV-3	0.0
CNS ca. (glio) SNB-19	3.3	Prostate	0.0
CNS ca. (glio/astro) U87-MG	0.0	Prostate ca.* (bone met)PC-3	0.0
CNS ca.* (neuro; met) SK-N-AS	0.0	Plancenta	0.0
Small intestine	0.1	Pituitary gland	0.5
Colorectal	0.1	Uterus	0.0

It is seen from Table 16 that there is high expression of sequence AL078594_A found in several ovarian cancer cell lines, and very high expression in normal adipose tissue.

Panel 2

Panel 2 consists of a 96 well plate (2 control wells, 94 test samples) composed of RNA/cDNA isolated from human tissue procured by surgeons working in close cooperation with the National Cancer Institute's Cooperative Human Tissue Network (CHTN) or the National Disease Research Initiative (NDRI). The tissues procured are derived from human malignancies and in cases where indicated many malignant tissues have "matched margins". The tumor tissue and the "matched margins" are evaluated by two independent pathologists (the surgical pathologists and again by a pathologists at NDRI or CHTN). This analysis provides a gross histopathological assessment of tumor differentiation grade. Moreover, most samples include the original surgical pathology report that provides information regarding the clinical stage of the patient. These matched margins are taken from the tissue surrounding (i.e. immediately proximal) to the zone of surgery (designated "NAT", for normal adjacent tissue, in Table 17). In addition, RNA/cDNA was obtained from various human tissues derived from human autopsies performed on deceased elderly people or sudden death victims (accidents, etc.).

These tissue were ascertained to be free of disease and were purchased from various high quality commercial sources such as Clontech, Research Genetics, and Invitrogen.

RNA integrity from all samples is controlled for quality by visual assessment of agarose gel electrophoresis using 28s and 18s ribosomal RNA staining intensity ratio as a guide (2:1 to 2.5:1 28s:18s) and the presence of low molecular weight RNAs indicative of degradation products. Samples are quality controlled for genomic DNA contamination by reactions run in the absence of reverse transcriptase using probe and primer sets designed to amplify across the span of a single exon.

Table 17.

Tissue Name	Rel. Expr. %	Tissue Name	Rel. Expr. %
Normal Colon GENPAK 061003	0.0	Kidney Cancer Clontech 8120607	0.0
83219 CC Well to Mod Diff (ODO3866)	0.0	Kidney NAT Clontech 8120608	0.0
83220 CC NAT (ODO3866)	0.0	Kidney Cancer Clontech 8120613	0.0
83221 CC Gr.2 rectosigmoid (ODO3868)	0.0	Kidney NAT Clontech 8120614	0.0
83222 CC NAT (ODO3868)	0.0	Kidney Cancer Clontech 9010320	0.0
83235 CC Mod Diff (ODO3920)	0.0	Kidney NAT Clontech 9010321	0.0
83236 CC NAT (ODO3920)	0.0	Normal Uterus GENPAK 061018	0.0
83237 CC Gr.2 ascend colon (ODO3921)	0.0	Uterus Cancer GENPAK 064011	0.0
83238 CC NAT (ODO3921)	0.0	Normal Thyroid Clontech A+ 6570-1**	0.0
83241 CC from Partial Hepatectomy (ODO4309)	0.0	Thyroid Cancer GENPAK 064010	0.0
83242 Liver NAT (ODO4309)	0.0	Thyroid Cancer INVITROGEN A302152	0.0
87472 Colon mets to lung (OD04451-01)	0.0	Thyroid NAT INVITROGEN A302153	0.0
87473 Lung NAT (OD04451-02)	0.0	Normal Breast GENPAK 061019	0.0
Normal Prostate Clontech A+ 6546-1	0.0	84877 Breast Cancer (OD04566)	0.0
84140 Prostate Cancer (OD04410)	0.0	85975 Breast Cancer (OD04590-01)	0.0
84141 Prostate NAT (OD04410)	0.0	85976 Breast Cancer Mets (OD04590-03)	0.0
87073 Prostate Cancer (OD04720-01)	0.0	87070 Breast Cancer Metastasis (OD04655-05)	0.0
87074 Prostate NAT (OD04720-02)	0.0	GENPAK Breast Cancer 064006	0.0
Normal Lung GENPAK 061010	0.0	Breast Cancer Clontech 9100266	34.6
83239 Lung Met to Muscle (ODO4286)	0.0	Breast NAT Clontech 9100265	100.0
83240 Muscle NAT (ODO4286)	0.0	Breast Cancer INVITROGEN	0.0

		A209073	
84136 Lung Malignant Cancer (OD03126)	0.1	Breast NAT INVITROGEN A2090734	0.0
84137 Lung NAT (OD03126)	0.0	Normal Liver GENPAK 061009	0.0
84871 Lung Cancer (OD04404)	0.0	Liver Cancer GENPAK 064003	0.0
84872 Lung NAT (OD04404)	0.0	Liver Cancer Research Genetics RNA 1025	0.0
84875 Lung Cancer (OD04565)	0.0	Liver Cancer Research Genetics RNA 1026	0.0
85950 Lung Cancer (OD04237-01)	0.2	Paired Liver Cancer Tissue Research Genetics RNA 6004-T	0.0
85970 Lung NAT (OD04237-02)	0.0	Paired Liver Tissue Research Genetics RNA 6004-N	0.0
83255 Ocular Mel Met to Liver (ODO4310)	0.0	Paired Liver Cancer Tissue Research Genetics RNA 6005-T	0.0
83256 Liver NAT (ODO4310)	0.0	Paired Liver Tissue Research Genetics RNA 6005-N	0.0
84139 Melanoma Mets to Lung (OD04321)	0.0	Normal Bladder GENPAK 061001	0.0
84138 Lung NAT (OD04321)	0.0	Bladder Cancer Research Genetics RNA 1023	0.3
Normal Kidney GENPAK 061008	0.0	Bladder Cancer INVITROGEN A302173	0.0
83786 Kidney Ca, Nuclear grade 2 (OD04338)	0.0	87071 Bladder Cancer (OD04718-01)	0.0
83787 Kidney NAT (OD04338)	0.0	87072 Bladder Normal Adjacent (OD04718-03)	0.0
83788 Kidney Ca Nuclear grade 1/2 (OD04339)	0.0	Normal Ovary Res. Gen.	0.0
83789 Kidney NAT (OD04339)	0.0	Ovarian Cancer GENPAK 064008	0.0
83790 Kidney Ca, Clear cell type (OD04340)	0.0	87492 Ovary Cancer (OD04768-07)	0.0
83791 Kidney NAT (OD04340)	0.0	87493 Ovary NAT (OD04768-08)	0.0
83792 Kidney Ca, Nuclear grade 3 (OD04348)	0.0	Normal Stomach GENPAK 061017	0.0
83793 Kidney NAT (OD04348)	0.0	NAT Stomach Clontech 9060359	0.0
87474 Kidney Cancer (OD04622-01)	0.0	Gastric Cancer Clontech 9060395	0.0
87475 Kidney NAT (OD04622-03)	0.0	NAT Stomach Clontech 9060394	0.0
85973 Kidney Cancer (OD04450-01)	0.0	Gastric Cancer Clontech 9060397	0.0
85974 Kidney NAT (OD04450-03)	0.0	NAT Stomach Clontech 9060396	0.5
		Gastric Cancer GENPAK 064005	0.2

There is high expression of sequence AL078594_A found in normal adjacent breast tissue and in breast cancer tissue. Panel 2 includes only two ovarian cancer samples, neither of which express this sequence.

Therefore, the FCTR2 protein of clone AL078594_A may serve as the target for a diagnostic assay in certain ovarian cancers, and as a potential therapeutic target for this subset of ovarian cancer and possibly for breast cancer.

The citation of any reference herein should not be deemed as an admission that such reference is available as prior art to the instant invention.

EQUIVALENTS

Although particular embodiments have been disclosed herein in detail, this has been done by way of example for purposes of illustration only, and is not intended to be limiting with respect to the scope of the appended claims which follow. In particular, it is contemplated by the inventors that various substitutions, alterations, and modifications may be made to the invention without departing from the spirit and scope of the invention as defined by the claims. The choice of nucleic acid starting material, clone of interest, or library type is believed to be a matter of routine for a person of ordinary skill in the art with knowledge of the embodiments described herein. Other aspects, advantages, and modifications considered to be within the scope of the following claims.